CHAPTER XIX

SYPHILIS OF THE NERVOUS SYSTEM

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Historical Introduction

The wide scope of such a subject as syphilis of the nervous system can best be estimated by the fact that there is scarcely a sign or symptom of a lesion of the nervous system, whether peripheral or central, that might not be caused by syphilis. The knowledge that syphilis is responsible for a large percentage of cases of organic disease of the nervous system has, however, been acquired only slowly.

Since the discovery of the specific organism by Schaudinn (1905) and the evidence of its invasion of the body in general and of the nervous system in particular, the knowledge of syphilis of the nervous system has been greatly advanced and extended. The history of the evolution of our knowledge of syphilis of the nervous system began with isolated observations of paralysis by several authors (Leoniceno, Van Hutten and Paracelsus) soon after the spread of syphilis in Europe and after the first great epidemic at the end of the fifteenth century. The earliest definite reference to syphilitic brain disease *appears to be* that given by Morgagni (1682–1771) when he states that gummata are not always found in the periosteum and bones but also in the brain. Moreover Morgagni in his Epistola Anat. Med. xxxii, Art. 28 (1761) describes not only aneurysms as occurring in syphilitic persons but also disease of the smaller vessels of the brain, which he observed in making a post mortem examination on a syphilitic man.

In the year 1740 Astruc in his book De Morbis Venereis refers several times to syphilitic lesions affecting the functions of the nervous system. It thus became recognized that syphilis could affect the internal organs including the nervous system. Then occurred a setback to our knowledge, for John Hunter about 1790 taught that the internal organs were not affected by syphilis; moreover he said, "We have not seen the brain affected, although such cases are described in authors." The weight of his great authority seems to have inhibited further reference to syphilis of the nervous system until in 1834 Lallemand presented a collection of syphilitic brain and nervous affections. Dittrich also showed that the liver was liable to be affected, and soon it became recognized widely that none of the internal organs, including the brain, are spared in syphilis. Then Virchow's teaching of the morbid histology of syphilitic gummatous lesions placed our knowledge of the disease on a sounder basis, with the result that numerous observers published observations and monographs on syphilis of the nervous system. Some of the more important contributions were made by Leon Gros, Lagneau, Lancereaux, Zambaco, Griesinger, Budd, Passavant, Steenberg, Wagner, Wilks, Hughlings

Jackson Mickle Gowers and Bristowe Clifford Allbutt in 1870 first described the microscopic characters of syphilitic disease of the arteries but it was Heubner who four years later published a classical monograph upon syphilitic disease of the cerebral arteries This was by far the most important and practical addition to our knowledge of syphilis of the nervous system since Virchow s description of the pathological anatomy of syphilitic gummatous lesions It was shown next by a number of authorities that not only acquired but hereditary syphilis affects the central nervous system producing the same pathological changes arterial disease and degenerations The names of Virchow Fournier Charcot Barlow Bury Ljungren and von Zeissl are associated especially with this advance in our knowledge of syphilis of the nervous system

Still another chapter had to be written that of the late degenerations the supposed primary decay of the neural elements as a result of the syphilitic infection formerly termed parasyphilitic or metasyphilitic affections The history of this will be given later but it is not out of place to mention the fact that Alfred Fournier was the first to express the view that locomotor ataxy is a postsyphilitic disease and Erb supported this doctrine of Fournier by his remarkable collected statistics extending over a period of twenty five years embracing 1 100 cases of tabes dorsalis and 10 000 nontabetic patients as a control Esmarch and Jessen and later Kjelberg were the first to call attention to the fact that general paralysis occurred especially in persons who had suffered with syphilis but it was Fournier who really put forward the doctrine that general paralysis was like tabes dorsalis a consequence of syphilis and that the two diseases were so similar in their etiology that they might probably be regarded as one disease affecting different parts of the nervous system Krafft Ebing at the International Congress held at Moscow related that nine well marked general paralytics with no history or physical scars of syphilis were inoculated with the virus of a hard chancre and watched for a long period without showing any further signs These experimental observations did more than anything el e to substantiate the syphilitic doctrine of Fournier Krafft Ebing put forward the dictum now widely accepted General paralysis is a product of syphilization and civilization In 1900 Mott reported twenty cases of juvenile general paralysis occurring in congenital syphilitics and reached the conclusion that syphilis was the essential cause in the adult for the clinical and anatomical conditions were identical A few years later Mott showed from a large collection of cases that tabes and general paralysis were one and the same disease affecting different parts of the nervous system and syphilitic in origin

Although nearly all neurologists and psychiatrists were arriving at the opinion that if there were no syphilis there would be no tabes or general paralysis it was not until the appearance of Noguchi and Moore s paper in February 1913 describing the existence of spirochetes in the brains of twelve out of seventy cases of general paralysis that the last link in the chain of evidence connecting the specific organisms directly with this disease was forged There are still many conditions as yet unexplained concerning these latent manifestations of syphilis of the nervous system but these will be discussed later

Pathological Groups of Syphilis of the Nervous System

The different clinical pictures presented by syphilis of the nervous system will be understood better when a full consideration has been given to the etiology pathogenesis and morbid anatomy Broadly speaking syphilitic diseases of the nervous system may be considered in two great groups I Interstitial or meningovascular neurosyphilis II Parenchymatous neurosyphilis

The interstitial forms are those in which there is a generalized or localized inflammatory reaction of the enclosing supporting and nutrient tissues of the central nervous system causing at first interference with and subsequently destruction of the nervous elements The symptom complex varies greatly but mainly depends upon whether the inflammation is (a) generalized or localized (b) causing vascular obstruction or occlusion (c) causing tumor formation and lastly (d) numerous observations of Oppenheim Somerling and Rosenteil indicate that the cranial nuclei are subject to a primary degeneration through the influence of syphilis These several morbid conditions may occur either singly successively and in severe untreated cases simultaneously The general symptomatology consequently is most variable and symptoms and signs may be presented of irritation or destruction of nervous tissues combined in cases of gummatous tumors with signs of increased intracranial pressure The clinical picture in untreated or imperfectly treated cases may be kaleidoscopic but essentially depends upon (1) the seat of the morbid process in respect to localization of function in the central nervous system (2) the existence of the above pathological conditions Thus we speak of cerebral and spinal syphilis yet in the majority of cases careful clinico anatomical investigation shows that the process has affected both brain and spinal cord and this is not surprising when the pathology of the disease is considered

Syphilitic diseases of the nervous system considered from a clinical as

well as from an anatomical point of view naturally fall into the two great groups of cerebral and spinal The cerebral may be subdivided into (a) basal meningitis (b) meningitis of the convexity (c) cerebrospinal meningitis (d) arteritis and (e) gummatous tumors These severally afford examples of groups of symptoms forming a definite clinical picture owing to the prominence of localizing physical signs The symptoms of arteritis are less definite unless there be vascular occlusion with consequent neural destruction Again localized gummatous tumors may occur causing in addition to irritative and destructive phenomena signs of intracranial pressure These conditions however may be more or less successively or simultaneously combined especially in those cases in which symptoms of infection of the central nervous system occur within the first few months or years after the appearance of the primary sore and which were not diagnosed or if diagnosed inefficiently treated

The lesions of the spinal cord are histologically similar to those of the brain There may be a generalized meningitis involving the roots and spreading along the pia-arachnoid septa to the medullary substance causing meningomyelitis The actual myelitis may be so extensive in one region as to cause a complete transverse lesion of the medulla according to the site of the myelitis a varying degree of loss of motor and sensory function occurs The inflammatory reaction may be acute or chronic it may subside in one region and become acute in another Endarteritis of spinal vessels nearly always is present to some degree and in some cases thrombotic occlusion takes place Lastly there may be an acute toxic myelitis These different anatomical lesions give rise to local or generalized irritation phenomena especially root symptoms are at first prominent but later if the disease spreads to the medulla complete or partial transverse lesions of tracts conveying afferent and efferent impulses to the brain occur causing very definite symptom complexes As in the case of the brain spinal cord diseases due to syphilis may be divided into groups upon an anatomical basis

It must be clearly understood that although syphilis of the central nervous system may be classified into cerebral and spinal forms because cases occur in which the cerebral or spinal symptoms are most obtrusive yet with an infective disease caused by the invasion of the central nervous system by the specific organism the active colonization of the organism in spinal and cerebral tissues respectively determines the symptom complex If the case be untreated the colonization which began initially in the brain or cord soon becomes generalized and a cerebrospinal syphilosis is the result

Interstitial or meningovascular syphilis of the nervous system therefore

will be dealt with under three headings according to the prominent symptom complex

1. Cerebral syphilis
2. Spinal syphilis
3. Cerebrospinal syphilis

Before passing to the more detailed account of syphilis of the nervous system a few remarks are necessary regarding parenchymatous neurosyphilis formerly called parasyphilis or metasyphilis. To this group belong the later manifestations of infection of the nervous system; they are insidious in their origin, progressive in character and comparatively less influenced by antisyphilitic treatment than meningovascular lesions. It should be clearly understood however that the term parenchymatous neurosyphilis is a general term used to designate the purely degenerative processes in the brain or spinal cord which has resulted from syphilitic infection and does not imply that these conditions are entirely free from associated meningovascular involvement. Etiologically and pathologically the parenchymatous affections are one and the same degenerative process, the result of toxins produced by the *Spirochæta pallida* affecting different parts of the nervous system. They may be classified clinically as follows:

1. Tabes dorsalis
2. Tabes optica
3. Taboparesis (taboparalysis)
4. General paresis (dementia paralytica or general paralysis of the insane)

ETIOLOGY

Spirochetal Invasion of the Nervous System

Since the discovery by Schaudinn and Hoffmann of the specific organism of syphilis, *Treponema pallidum* (*Spirochæta pallida*), a consideration of the etiology of syphilis of the nervous system must include some account of this organism, its probable biological nature and life history, also when, how and where it invades the central nervous system, as well as the natural defence mechanisms of the body.

The organism is a delicate spirillum, the number of coils varying from 6 to 20; there is a similar pointed extremity at each end and there is no differentiation of structure; the coils are uniform in size and the height about equal the breadth. It has been found in every possible lesion

which is definitely syphilitic in nature. Syphilitic lesions have been produced in animals by inoculation of material from all forms of human syphilitic lesions congenital or acquired viz the primary sore secondary lesions such as mucous tubercles and condylomata and even gummatous tertiary lesion. Spirochetes indistinguishable morphologically from those in the primary sore have been found in the brain in meningitis meningoencephalitis as well as in a large percentage of cases of general paresis or tabes dorsalis.

The *Treponema pallidum* is undoubtedly the specific organism of syphilis and the first question to be answered is What is its biological status? Is it a protozoon as Schaudinn believed but of which Metchnikoff was most doubtful or is it a bacterium? The answer is that it probably is neither the one nor the other but an organism belonging to a group the Spirochetoidea. According to Clifford Dobell who made a special study of the spirochete and related organisms the Spirochetoidea are non cellular organisms (Protista) and they undoubtedly belong to the schizophyta and not to the protozoa. The spirochetes differ from the bacteria in only one feature though actively motile they possess no organs of locomotion. Every other character which they possess is represented in other forms of bacteria. Some authorities are of opinion that *Treponema pallidum* is a protozoon as the following grounds

1 It produces the same perivascular infiltration with lymphocytes and plasma cells as occurs in sleeping sickness (trypanosomiasis). Against this however must be mentioned the fact that the tubercle bacillus invades the lymphatic system and produces a similar cellular reaction

2 It is claimed that the spirochete multiplies by longitudinal fission. This is not the case and the appearance of such a division is due to one spirochete becoming entangled with another. They divide by transverse fission. Histological study of the larger forms of spirochetes does not support this doctrine

According to McDonagh the actual cause of the infection is the spore of a coccidial protozoon and *Spirochæta pallida* is no more than the adult male phase of the life cycle. This view however has not yet been confirmed by biologists indeed some authorities are relinquishing the idea that *Spirochæta pallida* is a protozoon. There are certain facts however which appear to indicate that the spore forms may be one phase in the life history of the specific organism of syphilis the other being an intracellular or extracellular infective granule

Even in the later forms of parenchymatous neurosyphilis there is evidence to show that infection of the central nervous system may occur when the roseolar rash appears (secondary stage) and the question arises

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spirals were seen in some cases, whereas in others long forms predominated, they differed in no way morphologically from the forms met with in the primary or secondary lesions or in the organs of a child dying from congenital syphilis. Yet the experiments of Forster and Tomasczewski undoubtedly show that the spirochetes found in the small cylinders of brain substance of general paralytics removed during life fail to produce syphilitic lesions in rabbits when inoculated into the testicles or in apes when inoculated into the eyelid. These observers have made observations on sixty cases of general paralysis during life and obtained spirochetes in twenty-five per cent. of these cases. Their experiments on animals extended over several months, and although Noguchi and others have claimed to have produced a syphilitic meningoencephalitis in animals by repeated inoculations, yet the experiments carried out in Berlin by Forster and Tomasczewski clearly show that the organism in general paralysis either had become attenuated in its virulence and infectivity, or it was initially a functionally modified organism that invaded the nervous system. A. Marie and Levaditi claim to have infected rabbits by inoculating the testicles with the blood of a general paralytic. They believe in the existence of a special neurotropic organism in contradistinction to the dermatropic. There are some clinical facts which support this view, viz., one woman has infected several men, and these subsequently have developed general paralysis or tabes. Such cases may be explained by coincidence, but a striking clinical example supporting the theory of a neurotropic organism has been afforded by Brosius, who relates that seven glass blowers suffered with chancre of the lip, and out of five who ten years later came under observation four suffered with either tabes or general paralysis. In countries where syphilis has been introduced recently, general paralysis and tabes are not observed. Neisser taught that the widespread use of mercury might have modified the organism, while Mott considered that possibly a biological defence on the part of the organism had led to its taking refuge in the central nervous system.

When, how and where does the infection of the central nervous system take place? The secondary roseolar rash may be regarded as evidence of generalization of the specific organism in the blood and lymph streams of the body. The spirochetes are seldom found in the blood owing to its spirillocidal action. The development of spirochetal toxins causes cytological and biochemical changes in the blood; thus the polynuclear leucocytes are diminished, the lymphocytes increased, and further there is an increase of eosinophils. Before the generalization of the spirochetes in the body the blood serum fails to give a positive Wassermann reaction or the reaction is only partially positive.

whether there is a granule form of the spirochete which remains latent in the nervous system Wherever we find spirochetal infection of tissues and consequent cellular reaction whether the lesions that are examined be primary secondary tertiary or quaternary numbers of granules are found both free and contained in the cells These granules may be accounted for in two ways viz they may be the result of a granular plasmolysis of the spirochetes or they may be spores shed by the organisms If it could be proved that there is an infective granule phase of the specific organism of syphilis it would help to explain many facts regarding latent syphilis and the late manifestations of neurosyphilis So far however there is no certain proof of the existence of an infective granule although there are indications Thus Neisser was able to inoculate monkeys by using bone marrow of a syphilized animal in which the most diligent search revealed no spirochetes

The observations of O Farral and A Balfour showed that the injection of salvarsan had the effect of causing a shedding of granules but that this also occurred independently of the action of any drug This phenomenon is not confined to the specific spirochete of syphilis it occurs in other forms met with in the primary sore The arsphenamines increase the granule discharge and O Farral and Balfour considered that the discharge was protective the granules being of the nature of resistant spores the further history of which remains unknown but which so far as those derived from *Treponema pallidum* are concerned doubtless play an important part in relapses The important researches of Leishmann on the spirochete of tick fever showing that in this disease there is an intracellular phase of the spiral organism in the form of chromidian granules support the hypothesis of a latent resistive granular intracellular form Until however we can see the spiral forms undergoing spore formation and the spores developing into spirals the proof is wanting and all the granules whether intracellular or extracellular can be explained by the defensive reaction of the fluids and tissues of the body upon the spirochetes Mott's observations on the spirochete in the brains of 100 cases of general paralysis in which the organism was found in 66 led him to think that there was no spore formation for although he saw in smears and sections spirochetes in which the spiral form had been completely or almost completely lost (straight forms) in which an appearance like spore formation occurred in silver stained preparations yet he came to the conclusion that these more probably were degenerative forms in the first stage of plasmolysis Mott was not able to satisfy himself of the existence of intermediate forms either intracellular or extracellular Although short forms of spirochetes with relatively fewer

that between August 1911 and September 1913 302 cases were admitted to Chatham Hospital and diagnosed as chancroid or venereal sore of doubtful nature. Of these no less than 255 later proved to be syphilitic by the finding of the spirochete, a positive Wassermann reaction or by development of secondary symptoms. Before the modern methods of diagnosis were known it was the custom in doubtful cases to wait until secondary symptoms manifested themselves before placing the patient on treatment. Generalization in the blood and lymph streams however had occurred already, consequently the possibility of infection and colonization in the central nervous system had not been averted. Experience has shown that it is often the mild cases of primary and secondary syphilis which afterward may develop the later parenchymatous forms. Indeed it is the exception to find a case that suffered with marked skin lesions develop general paresis or tabes dorsalis.

Too often either from neglect by the patient or carelessness on the part of the doctor only a short course of treatment was given, the result being that in a certain number of cases where the nervous system had been infected nervous disorder followed. This argument however does not apply to those cases which developed late manifestations even after prolonged courses of mercurial treatment. Moreover cases have now been recorded in which parenchymatous neurosyphilis has developed in spite of arsphenamine treatment. Statistics tend to show that the average time for the appearance of tabes and general paresis is ten to fifteen years no matter whether the cases belong to those which have received treatment or not. It would appear therefore that the success of a prolonged course of treatment in respect to the prevention of neurosyphilis, particularly the late parenchymatous forms, depends as much upon when the treatment was begun as upon its efficiency and continuance. Now with increased knowledge and experience it is reasonable to hope that all forms of neurosyphilis, early as well as late, have diminished in proportion to the practice of prophylaxis by early self-disinfection and to the efficiency of early diagnosis followed by early intensive treatment.

Contributory Causes

All causes which tend to produce a locus minoris resistentiæ in the nervous system will predispose to the onset and progress of syphilitic affections. Thus alcoholism, lead and other toxic conditions, head and spinal injuries, sexual excesses, violent emotional disturbances, prolonged anxiety, worry and excitement with associated insomnia all tend to act as

Occasionally as first pointed out by Lang and as we ourselves have observed quite early in the disease even before the primary sore is healed symptoms indicating meningitis may occur Some of the most intractable cases of cerebral and spinal neurosyphilis develop within the first twelve months after infection it is, therefore quite probable that the meninges were infected at the time of the roseolar rash in many of these cases but the nervous symptoms occurring then were slight and overlooked Occasionally severe symptoms of meningitis have occurred within a few months of the primary sore Fordyce holds the same view and cites the researches of Warthin who found that in visceral syphilis spirochetes may be present for years without producing reactive phenomena Also the results of numerous observers show that from twenty five to thirty five per cent of patients in the first year show pathological changes in the cerebrospinal fluid In some of these patients after minor damages to the meninges cerebrospinal tracts or cells the infection may disappear spontaneously or be cured by treatment This is shown in cases of mild tabes with pupils irregular unequal or inactive to light but active in accommodation together with slightly altered or absent deep reflexes with negative Wassermann reaction in blood and cerebrospinal fluid

The persistence of a positive Wassermann reaction in the cerebrospinal fluid after treatment has caused it to disappear from the blood suggests the existence of the specific organism in the nervous system None of the specific remedies arsenic bismuth or mercury will pass through the choroid plexus consequently not entering the cerebrospinal fluid which irrigates the central nervous system their administration has but little effect upon the life of the organism when it has left the lymphatics in the wall of the blood vessels and entered the perivascular and perineuronal spaces containing the cerebrospinal fluid

The Influence of Early Diagnosis and Treatment

The very satisfactory results obtained by modern efficient early treatment of syphilis in the primary stage leads one to hope that infection of the nervous system can be prevented In the past many of the more serious cases of neurosyphilis were those in which the primary sore was so indefinite as to have been overlooked or forgotten by the patient or if a practitioner had been consulted it was regarded by him as a soft sore and only local treatment employed Of the danger of infection of the nervous system from this cause we have the evidence before the Royal Commission on Venereal Disease of Surgeon Scott of the Navy who states

tures which have anatomical lymphatic relations with the central nervous system may play an important part in causing neurosyphilis and determining the initial localization of the morbid process. Energetic treatment in the secondary stage may prevent this secondary colonization in the nervous system from occurring. Why an individual who is infected suffers with meningovascular neurosyphilis while another suffers with parenchymatous neurosyphilis may be explained either by a modification of the virus in the latter or by a difference in the resistance of the individual. This subject will be dealt with more fully in the discussion on the etiology of parenchymatous neurosyphilis.

Gummatous Tumors

Gummatous tumors may start in an osteitis or periostitis of the skull or spinal column and extend to the adjacent membranes. Gummata, however, generally begin in the membranes and usually it is difficult to decide whether the growth had its origin in the dura or the leptomeninges, as frequently all are adherent to each other in the process. Sometimes a syphiloma starting in the meninges extends outward and involves the skull, but the gummatous process starting in the meninges invariably extends along the pia-arachnoid sheaths of the vessels into the substance of the brain. A gumma of the base of the brain almost always begins in the pia-arachnoid and seldom involves the dura mater.

Upon opening the cranial cavity and removing the skull cap, a gummatous tumor may be recognized by certain naked-eye appearances and characteristics. There is an elevation of the dura mater if it be situated on the convexity; it may be pinkish from congested vessels or grayish yellow, or both, and the surface irregular and nodular. To the touch it may be tough and resistant in one part and soft and succulent in another. On slitting the dura and endeavoring to expose the brain surface, it will be found that a close adhesion of all the membranes to the brain exists at the site of the tumor and generally for some considerable area adjacent. The gummatous tumor seldom is single; its usual size is from one to four centimetres in diameter, but it may be as small as to measure only a few millimetres in all directions or as large as six centimetres in diameter. Its consistency varies in different parts, likewise its color, and this is easily explicable when its microscopic structure is understood. It has an irregular, nodular, warty surface, which at one part may appear pink, at another grayish pink or grayish, at another yellow or grayish yellow. At some places it feels succulent, at others firm and tough. On section areas of caseous yellow material may be seen interspersed with gray

contributory coefficients in the production of nervous disease especially the late degenerative parenchymatous forms of syphilis where the organism presumably is latent A severe blow on the head may cause a gummatous tumor to form in the subject of syphilis or may precipitate mental symptoms in an incipient general paretic in both instances, it may be presumed that the organism exists in a latent form

Incidence of Nervous Syphilis

A communication by Mattauschek and Pilcz is of interest as regards the liability of infected persons to suffer later from neurosyphilis It relates to the incidence of syphilis of the nervous system in 4 184 officers infected between the years 1880 and 1900 Of these 198 died of general paralysis 116 of tabes and 134 of cerebrospinal syphilis These figures give about ten per cent of men infected who although treated by mercury subsequently died of syphilis of the nervous system Boulloche found in an analysis of 1 085 cases of syphilis of the nervous system mostly under the care of Fournier that there were 77 cases of spinal syphilis and 416 cases of cerebrospinal syphilis Nonne in 185 cases of neurosyphilis found 128 cases of cerebral syphilis and 29 of spinal syphilis The arterial form occurred in 43 cases the meningeal in 128 and the remaining 14 were a combination of both forms

Morbid Anatomy

The nervous system may be infected simultaneously with the generalization and secondary eruption on the mucous membranes and skin Numerous observations have shown that a meningeal reaction manifested by an increased cell and protein content in the cerebrospinal fluid is found often in early syphilis Plaut has shown that as soon as a positive Wassermann reaction appears in the blood in primary syphilis changes are present in the cerebrospinal fluid in 84 per cent of untreated cases These changes reach a maximum during the secondary stage of the disease *and probably disappear subsequently in the majority of instances* This early meningeal reaction does not necessarily indicate the probability of later nervous sequelæ but in this respect a meningeal reaction in long standing syphilis is of more serious import The central nervous system may be infected subsequently from spirochetal foci in the peripheral nerves along lymphatics to the cerebrospinal axis by perivascular lymphatics from spirochetal foci in the aorta lymphatic glands or other infected structures Chance colonization of the specific organism in struc

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tures which have anatomical lymphatic relations with the central nervous system may play an important part in causing neurosyphilis and determining the initial localization of the morbid process Energetic treatment in the secondary stage may prevent this secondary colonization in the nervous system from occurring Why an individual who is infected suffers with meningovascular neurosyphilis while another suffers with parenchymatous neurosyphilis may be explained either by a modification of the virus in the latter or by a difference in the resistance of the individual This subject will be dealt with more fully in the discussion on the etiology of parenchymatous neurosyphilis

Gummatous Tumors

Gummatous tumors may start in an osteitis or periostitis of the skull or spinal column and extend to the adjacent membranes Gummata however *generally begin in the membranes and usually it is difficult to* decide whether the growth had its origin in the dura or the leptomeninges as frequently all are adherent to each other in the process Sometimes a syphiloma starting in the meninges extends outward and involves the skull but the gummatous process starting in the meninges invariably extends along the pia arachnoid sheaths of the vessels into the substance of the brain A gumma of the base of the brain almost always begins in the pia arachnoid and seldom involves the dura mater

Upon opening the cranial cavity and removing the skull cap a gummatous tumor may be recognized by certain naked eye appearances and characteristics There is an elevation of the dura mater if it be situated on the convexity it may be pinkish from congested vessels or grayish yellow or both and the surface irregular and nodular To the touch it may be tough and resistant in one part and soft and succulent in another On slitting the dura and endeavoring to expose the brain surface it will be found that a close adhesion of all the membranes to the brain exists at the site of the tumor and generally for some considerable area adjacent The gummatous tumor seldom is single its usual size is from one to four centimetres in diameter but it may be as small as to measure only a few millimetres in all directions or as large as six centimetres in diameter *Its consistency varies in different parts likewise its color* and this is easily explicable when its microscopic structure is understood It has an irregular nodular warty surface which at one part may appear pink at another grayish pink or grayish at another yellow or grayish yellow At some places it feels succulent at others firm and tough On section areas of caseous yellow material may be seen interspersed with gray

strands of fibrous tissue these are especially noticeable in the central parts of the tumor which may consist entirely of this caseous material enclosed in a dense fibrous capsule More often however there is an intermingling of caseous foci gray strands of dense fibrous tissue and more succulent pinkish gray tissue Often the circumference of the tumor presents a vascularity which affords a striking contrast to the central non vascular fibrous and necrotic parts Microscopic examination affords an explanation of this variegated appearance of the neoplasm for if we examine microscopically a recent syphiloma the variegation is seen to be due to an increased vascularity in parts there is no caseous material corresponding to older parts of a growth which have undergone necrobiosis the neoplasm consists essentially and primarily of a granulation tissue formed by the active proliferation of the connective tissue and endothelial cell elements it is a mass of embryonic cells lymphocytes and plasma cells filling up all the interstices of the groundwork of connective tissue cells But these embryonic cells by the rapidity of their formation and consequent compression of the vessels suffer from denutrition and undergo necrobiosis leaving behind a dry granular amorphous mass of detritus containing but few fat globules and not proceeding to calcification In the neighborhood of the caseous focus may be seen a number of plasma cells and lymphocytes which are undergoing necrobiotic change in other parts there are strands or even a capsular formation of fibrous tissue consisting of spindle cells and stellate cells sometimes this tissue has proceeded to form dense scar tissue or it is more succulent and it then consists of connective tissue cells in the meshes of which are numbers of lymphocytes and plasma cells Such tissue is likely to be seen at the growing edge or where it is extending along the pial sheath into the brain substance usually it is highly vascular and contains new sprouting capillaries which vessels frequently take the form of a crown surrounding the central older non vascular portions of the neoplasm Giant cells have been described by various authors including Baumgarten who however has formed the opinion that the finding of giant cells points to a mixed infection with tubercle The only case in which Mott found giant cells was one of multiple gummata and here there was undoubtedly secondary tuberculous infection for bacilli were found in the giant cells

Diffuse gummatous meningitis and arteritis are usual accompaniments of gummatous tumors Arteries in the gummatous mass have walls thickened by subendothelial cell infiltration going on to fibrosis which may cause vascular occlusion leading to ischemic necrosis In large old gummatous tumors of the base of the brain and surrounding branches of the circle of Willis the existence of arteries in the tumor mass may be

manifest only by the crinkled outline of the elastic lamina upon micro scopic examination

Circumscribed gummata may occur in any region of the brain or spinal cord but there are certain regions in which they are more frequent Thus they have a predilection for the base of the brain especially the optic chiasma and the interpeduncular space they may involve any one of the cranial nerves especially the third nerve another site for circum scribed gumma is around one of the arteries of the circle of Willis espe cially the middle and anterior cerebral Gummata also occur on the convexity of the brain and the seat of predilection is either the frontal or parietal region but no portion of the central nervous system can be said to be exempt *It is a remarkable fact that whereas gummata of the* superficial parts of the body rapidly disappear with antisyphilitic treat ment gummatous tumors of the brain do not undergo resorption so readily It is probable that such neoplastic formations are not treated early enough and a certain degree of tissue necrobiosis and hyperplastic fibrosis may have taken place already before antisyphilitic remedies are employed Even when the active neoplastic formation is arrested a fibrous tissue scar must remain which if it has not produced enough nerve cell and fiber destruction to cause serious loss of function can nevertheless act as a continuous source of neuronic disturbance and occasion epileptiform seizures

Meningitis

A diffuse gummatous meningitis may affect all three membranes or be limited *to the soft membranes When the morbid process spreads* from a syphilitic osteitis or periostitis to the dura mater it produces a *fibrous hyperplasia of the dura so also when the disease starts in the* membranes of the convexity a fibrohyperplastic meningitis results *Under these conditions the dura mater is several times thicker than* normal and it forms adhesions with the subjacent thickened and in filtrated soft membranes This is termed gummatous pachymeningitis and it is often but not invariably associated with some degree of meningo encephalitis

A section of the cortex usually will show as in the case of the cir cumscribed gumma infiltration of the perivascular sheaths with lympho cytes and plasma cells extending a variable distance into the substance of the brain along the pial sheaths there are also thickening and prolifera tion of the connective tissues of the meninges with fibrous hyperplasia especially in the superficial dural layers infiltration with lymphocytes

and plasma cells especially of the pia arachnoid and congested vessels and infiltration of the walls with embryonic cells There is always some periarteritis frequently an endarteritis and usually a neuroglia cell hyperplasia which may be marked There is disorganization or complete destruction of the columns of Meynert The ganglion cells which are not destroyed stain poorly and exhibit a breaking up or disappearance of the Nissl granules A variable degree of damage or destruction of the medullated fibers is shown In old lesions the neural substance may be replaced by a network of fibers and branching neuroglia cells

The most frequent form of syphilitic meningitis is confined to the leptomeninges and the dura mater is not involved The seat of predilection is the base of the brain Basal syphilitic meningitis is the earliest and most frequent result of spirochetal invasion of the central nervous system frequently it is followed or accompanied by an extension to the spinal meninges and sometimes by an extension to the convexity of the brain

This disease generally is associated with periarteritis and endarteritis and in fatal cases with multiple gummatous tumors which may be found in various parts of the brain When the meningitis extends down the spinal canal not only are the cranial nerves involved in the neoplastic formation but also the spinal nerve roots In such cases there is in fact a generalized cerebrospinal meningitis The seat of preference however is the interpeduncular space and optic chiasma The whole base of the brain and spinal cord in severe cases appears covered with an exudation filling up the fissures sulci and crevices surrounding the vessels nerves and nerve roots with a semi solid substance as if gelatin or agar culture medium had been poured over and allowed to set It is very rarely purulent when it is so a secondary microbial infection may be anticipated The neoplastic formation may have a grayish appearance in some areas in others it may appear speckled yellow or pinkish gray the former indicative of fibrous sclerous formation the latter of necrobiotic change Sometimes miliary or warty elevations occur which may be either fibrous or caseous or there may be multiple nodular gummatous tumors scattered all over the under surface of the brain

Microscopic examination reveals the same morbid change observed in the circumscribed gumma There is an infiltration of the leptomeninges with lymphocytes and plasma cells this infiltration surrounds all the vessels and their pial sheaths which extend into the substance of the central nervous system the infiltration invades the walls of the vessels and produces a thickening of the coats Appearances suggest that the infiltration commences in the perivascular lymphatics The round-celled

infiltration extends into the perineurium and endoneurium of the cranial and spinal nerves The optic nerves the chiasma and optic tract the motor nerves of the eyeball any or all of the cranial nerves and spinal nerves may show a variable degree of infiltration and give an anatomical basis for the involvement of the various nerves as is seen clinically so often in patients with this type of disturbance

In meningomyelitis the inflammatory reaction may be localized in its intensity and spreading to the medullary substance give rise to a transverse focal myelitis The symptoms depend upon the situation but the pathological process is the same a secondary degeneration of ascending and descending tracts terminating in sclerosis results A sclerosis or induration of the brain associated with atrophy and defective development of the neural structures may result from a syphilitic meningitis with a diminution but not abolition of the vascular supply This sclerosis is met with also in congenital syphilitic children and usually is associated with a mental deficiency amounting to either idiocy or imbecility

Disease of the cranial nerves is in the great majority of cases secondary to a meningitis but occasionally it is primary and gummatous neuritis of a single or of several cranial nerves may occur also there may be as in a case recorded by Kahler a multiple syphilitic neuritis affecting the greater part of the cranial nerves and the spinal roots The cranial nerves may be affected also by compression of gummatous tumors and by aneurysmal dilatation of vessels

Arteritis

The older writers as already mentioned described arterial changes in syphilis and again Sternberg in 1860 drew attention to the causal relationship of syphilis and arterial disease Ten years later Allbutt described the microscopic changes in syphilitic arteries It was Heubner s classical monograph in 1874 however which showed that endarteritis syphilitica was of overwhelming importance in cerebral syphilis and in the explanation of its symptomatology Heubner divided syphilitic vascular affections into three groups (1) arterial disease as the result of an extension of a syphilitic gummatous process to the wall of the vessel thereby causing damage by compression or by extension of the process to the wall of the vessel (2) arterial disease existing independently of but associated with a syphilitic neoplastic formation (3) arterial disease existing independently of gummatous meningitis

The naked eye change is very characteristic The arteries instead of being thin transparent and collapsing between the fingers and thumb are

firm cylindrical and cannot be compressed into a flat condition They may have a grayish yellow appearance like dirty washleather but usually this is not uniform sometimes branches or parts of an artery appear yellow or dirty white or grayish yellow nodules gradually fading off into grayish pink are seen scattered on the main arterial trunks or on their larger branches Upon transverse section the whole arterial wall may be firm and cut readily showing the lumen partially or nearly wholly obliterated by the thickened wall In the smaller arteries the lumen usually is uniformly obliterated in the larger arteries the wall may present a nodular thickening so that when cut transversely the thickened uncollapsible portion of the arterial wall has a half moon shape and a grayish yellow color The vessels at the base of the brain are particularly liable to show this endarteritis and all the vessels of the circle of Willis and its branches may be more or less affected

Careful examination of the cerebral vessels in a large number of cases of syphilis of the central nervous system convinced Mott that the arterial system invariably is affected to some degree by an endarteritis it may be slight and random there being only a few nodules scattered here and there in the arteries or there may be found an abundance of areas of endarteritis These scattered patches and nodules of endarteritis found especially in the larger arteries of the base of the brain may or may not be accompanied by obvious meningitis Sometimes they form part of a morbid picture of a universal syphilitic endarteritis again not necessarily associated with obvious meningitis

These facts support the view that spirochetal infection of the lymphatics of the adventitia of the arteries is the cause of the endarteritis Owing to the course of the lymph stream corresponding in direction to the blood stream an arterial lymphogenic infection occurs consequently the arteries of the base are especially affected The localized nodular character of the lesions affecting arteries of the base of the brain would be against its being due to a generalized spirochetal toxin effect on the lymph stream but rather as in the case of nodular aortitis it would point to a spirochetal insemination and subsequent colonization in an area corresponding to the perivascular lymphatics of arteriæ arteriorum This would give rise to an inflammatory reaction in a corresponding vascular area of distribution The lymphocyte infiltration especially around the vasa vasorum of the middle coat is evidence of a localized inflammation which causes weakening of the muscular coat The localized thickening of the endarterium by proliferation of the fixed connective tissue cells of the subendothelial layer may be explained either by an irritative hyperplasia occasioned by the syphilitic toxin or

by the weakened muscular coat causing a compensatory fibrous tissue hyperplasia and when there is a generalized obliterative endarteritis affecting the arteries of the convexity as well as the base we must regard this as evidence of a generalized distribution of the specific toxin in the lymphatics of the cerebral arteries causing the same reactions as when it is localized Usually in such conditions there is evidence of a generalized periarteritis as well as endarteritis Another effect of a localized inflammation and weakening of the wall of an artery by syphilis is the formation of intracranial aneurysms In a case of syphilitic arteritis that died in Claybury Mental Hospital Mott found multiple aneurysms of the cerebral vessels as well as an aneurysm the size of a filbert on each internal carotid just at the bifurcation of the common carotid

Heubner asserted that syphilitic arteritis does not end in fatty degeneration or calcification and therefore does not cause atheroma A fibrous sclerosis undoubtedly is the usual terminal stage of syphilitic endarteritis but Heubner s statement is too exclusive and the researches of Oedmannson confirmed by Birsch Hirschfeld upon the atheromatous changes in the umbilical vessels and in the arteries of premature still born syphilitic fetuses support the contention that atheroma may occur as a result of the action of the syphilitic virus All the pathological conditions which have been described result from congenital as well as acquired syphilis Internal hydrocephalus as a result of basal meningitis is however more common in congenital than acquired syphilis

The morbid anatomy of parenchymatous neurosyphilis will be considered later as there are certain special features which differentiate it from the meningovascular conditions above described

Symptomatology of Syphilis of the Brain

There is nothing actually specific in the symptomatology of cerebral syphilis and yet just as in the consideration of the pathological conditions there is a general grouping of phenomena which renders it almost certainly characteristic so also is this true in the symptomatology

It is characteristic of neurosyphilis to resemble in its symptom complex a number of serious organic diseases of the nervous system and yet not be identical with them Even the same case may simulate a number of these diseases at different periods in its progress and competent authorities may make very different diagnoses of such cases owing to this variability Thus at one time a patient may present the signs of meningitis but owing to the fact that the arteries may be affected or that there may be an associated intracranial tumor formation the symptoms more

resemble cerebral softening meningitis or tumor The same case may present at one time the clinical picture of epilepsy of meningitis of intracranial tumor of general paresis or of a dementia with organic brain disease and paralysis

The kaleidoscopic characters manifested by a severe and fatal case of cerebral syphilis can be well understood if a complete macroscopic and microscopic examination of the brain be made Examinations made by Mott of fifty such cases dying in mental hospitals showed meningitis arteritis softenings and gummatous tumors scattered in the central nervous system in various stages of evolution and devolution

Basal Meningitis

Obviously the important anatomical structures existing at the base of the brain must have a significant relationship to the symptom complex met with in this form of neurosyphilis Firstly there is the circle of Willis which apart even from endarteritis is certain to be affected to some degree by a periarteritis which will extend along the perivascular sheaths into the whole of the important structures forming the base of the brain then there are the basal ganglia the internal capsule the peduncles and pons and medulla with their important cranial nerve nuclei Again all the cranial nerves including the olfactory and especially the optic nerve chiasma and tract are liable to be involved in the diffuse gummatous formation or to be the seat of gummatous tumors Although there is a general similarity in all cases of basal meningitis and especially as regards certain symptoms yet there are infinite possibilities of variation in different cases and even variability in the clinical picture manifested by the same case at different periods of the disease

Symptoms of Basal Meningitis — *Headache* very rarely is absent and may precede all other symptoms by weeks months or years The pain is paroxysmal and when it reaches its greatest intensity may be boring splitting stabbing or throbbing this may die down in the intervals leaving only a dull aching sensation

The pain causes sleeplessness loss of appetite and general failure of health The headache may be more severe at night and wake the patient up at an early hour in the morning There is no tenderness at any particular spot on pressure or percussion as there is in meningitis of the convexity When however the fifth nerve or the Gasserian ganglion is involved there may be a general hyperesthesia in the area of distribution of the nerve and the condition may be mistaken for trigeminal neuralgia

The headache usually is referred to the frontal parietal or temporal re gions and is deep seated and cannot be definitely localized later on it may spread to the occipital region the neck and the spine sometimes pain is referred to the back of the eye

Vertigo reeling and *staggering* are common symptoms Doubtless some of the attacks of giddiness from which such patients suffer are dis turbances of consciousness slight fainting attacks are due to circulatory disturbances of the brain from the associated arterial affection These attacks may be mistaken for attacks of petit mal or migraine

Vomiting is a fairly constant symptom and together with headache may for months form the only signs of cerebral disease it may occur without relation to meals Oppenheim mentions a case in which for months it preceded headache and other symptoms in this case there was a widespread gummatous meningitis in the posterior cerebral fossa In some cases however vomiting has been absent throughout the whole course of the disease to the fatal termination

Fever There is considerable difference of opinion by authorities as to the existence of pyrexia as a result of syphilitic basal meningitis Fever may occur at the onset of symptoms in some cases but as a rule it is not high perhaps one or two degrees above the normal and it does not persist The temperature usually is normal and sometimes subnormal If pyrexia is present it is of an anomalous form and usually due to complications it may be remittent and sometimes at the onset of the disease there may be a rise of temperature in the evening

Polydipsia and Urinary Changes Sometimes excessive thirst and the passage of large quantities of pale urine of low specific gravity may be a pronounced symptom during the whole course of the disease (diabetes insipidus) more often this condition exhibits remissions Diabetes mel litus is met with occasionally

Psychical Disturbances No symptoms play a more important role in the symptomatology of cerebral syphilis especially the basal form of disease than the disturbances of consciousness Combined with stupor which is like that met with in many cases of cerebral tumor are other manifold disturbances of consciousness

A very characteristic sign of basal syphilitic meningitis is the semi somnolent *semiconscious semicomatose condition in which the mental* functions are more or less obfuscated rather than obliterated The patients may present a lethargic typhoidal or semi intoxicated condition from which they can be aroused temporarily a condition which is how ever frequently combined with a purposeless hazy motor delirium not of a purely automatic character Even in the lesser degrees of impaired

consciousness there are certain criteria of especial significance Thus a patient may be roused to answer questions more or less correctly in a slow drawling and sleepy manner He may even perform complex acts in response to requests or demands yet be unable to respond to the calls of nature and he passes urine and feces in the bed or on the floor in the room Occasionally the patient may masturbate shamelessly The mind again may become clear and he may regain control but not infrequently this loss of control over the sphincters persists and this may denote the onset of dementia The dementia of interstitial cerebral syphilis is characterized by being partial and recurring in attacks it does not alter the character and personality of the individual to the same extent as in the dementia of general paresis He preserves his autocritical faculties and is conscious of his intellectual deficit and he is by no means indifferent to his mental and bodily condition He may suffer from loss of memory especially of recent events and his knowledge of time and place may be defective He is subject to sudden fits of excitement with motor restlessness or of depression with suicidal tendencies

In some cases consciousness remains for a long time undisturbed and the patient suddenly may become comatose and die Cases recorded by Buzzard Althaus Rumpf and Fournier show that coma may be the sole symptom of a fatal cerebral syphilis But a deep coma may on the other hand disappear and the patient become semiconscious or even completely recover consciousness Another noteworthy phenomenon is a drowsy condition which may deepen into a semiconscious state from which he can be awakened only to return to a state of deep comatose lethargy

All gradations of loss of intelligence and impairment of memory are to be met with in these cases but during the course of the disease marked oscillations and remissions of the mental symptoms may occur Patients not infrequently are sent to mental hospitals who have been taken up by the police because found wandering at large or because they have committed acts dangerous to themselves or others They may have delusions and hallucinations which when combined with motor restlessness and tremor alternating possibly with a semi intoxicated drowsy stupor present a clinical picture not unlike delirium tremens Again they may have delusions of being followed or of persecution or of poisoning which may incite them to acts of violence As alcohol often is associated with the onset of the symptoms the condition may be put down to alcoholic intoxication unless some obtrusive paralytic symptom for example an oculomotor paralysis makes one suspect an organic brain disease These insane conditions may alternate with stuporous semicomatose attacks

and with various degrees of return to normal states of consciousness in which the intelligence is not seriously impaired

Convulsive Attacks General convulsions of an epileptiform character unilateral or partial epileptiform seizures are not infrequent and Mott mentions a case in which tetaniform spasm and opisthotonos occurred the meningitis was found post mortem to have affected the posterior fossa and the spinal cord General tremor is met with not infrequently in severe fatal cases

If recovery from basal syphilitic meningitis occurs some degree of mental impairment may result and even if there are no gross symptoms of mental degeneration there may be some slowness of ideation and verbal expression combined with lack or deficiency of control and purposeless outbursts of temper or fits of anger There is sometimes a lack of facial expression or a fixity of gaze and such patients are liable to show epileptiform manifestations

Eye Symptoms In describing the pathology of the disease it has been pointed out that the optic chiasma and interpeduncular space are sites of predilection for gummata and diffuse gummatous meningitis Consequently visual troubles of all kinds up to complete blindness and partial or complete oculomotor paralysis are among the commonest symptoms in this form of neurosyphilis The observations of early authors on cerebral syphilis showed how frequently affections of the cranial nerves and motor and sensory tracts occur the oculomotor nerves are especially liable to be affected Von Graefe in 160 cases found that in more than one half there was some form of oculomotor paralysis Alexander found that in 727 cases there was unilateral paralysis partial or complete of the oculomotor nerve and both Ricord and Fournier designate this ophthalmoplegia la signature de la vérole The important significance of eye affections in cerebral syphilis is emphasized strikingly by Uhthoff s observations he found that only in about fifteen per cent of all cases of cerebral syphilis were eye affections completely absent during the whole course of the disease

Cerebral syphilis may be accompanied by the following ophthalmoscopic changes (1) optic neuritis (2) papillœdema (choked disc) (3) optic atrophy In the greater number of cases of cerebral syphilis these conditions are associated with a basal meningitis Papillœdema when present almost always affects both eyes whilst neuritis may remain limited to one eye The former condition is due to tumor formation (gumma) which may be situated anywhere in the cranial cavity consequently the general increase of intracranial pressure caused by their presence affects both eyes fairly equally Optic neuritis however is due

to the extension of the gummatous inflammation first to the sheath and then to the optic nerve itself It is limited often to one side during the whole course of the disease and when both are affected there is generally in contradistinction to the papilledema a very considerable difference in the intensity of the neuritis in the two eyes Owing to the external situation of the macular bundle of fibers a central scotoma may arise as a consequence of a gummatous process setting up a retrobulbar neuritis of these fibers

If the gummatous process (meningitis) extends primarily to the optic chiasma and optic tracts considerable visual disturbances may occur without any observable changes in the fundus It is not only necessary, therefore to make an examination with the ophthalmoscope but to test the fields of vision with the perimeter and to chart the results if the patient is in a fit condition for the examination According to the experience of Oppenheim and others hemianopsia is fairly frequent and usually is due to the optic chiasma being involved It may arise however from softening of the optic radiations caused by arterial thrombosis or from the existence of a large gumma or softening in the occipital lobe

A gummatous process at the base of the brain can produce by extension a localized neuritis or perineuritis of the optic nerve fibers and cause a neuritis descendens In the stem of the optic nerve the fibers to the macular region run at the periphery and a perineuritis naturally will damage the outermost fibers first causing thereby a blurring or scotoma of the central portion of the visual field On the other hand when the central parts of the optic nerve are affected the defect will be most marked in the peripheral field of vision In most cases where the gummatous process has attacked the nerve there remains a variable proportion of the optic fibers still functionally intact consequently all grades of partial blindness may occur but in some cases the whole of the optic fibers may be destroyed and the result is complete blindness It will be easily seen that all possible forms of limitation of the visual field and of central scotoma may arise and from the foregoing remarks it will be understood why irregularity in the defects of the visual field is a noticeable feature in syphilitic brain disease

Third Nerve Affections Of all the cranial nerves the oculomotor nerve is affected by far the most frequently it may be affected on one side or on both sides and completely or partially The muscle specially liable to be paralyzed also the earliest to be affected is the levator palpebræ causing ptosis in fact this condition always should make one think of the possibility of syphilis apart from any other symptom Occasionally the pupil only is affected it is often dilated on one side

and fixed to light and accommodation sometimes only the light reflex is lost and Mott mentions two cases in which both oculomotor nerves were completely paralyzed

Oppenheim states that in 17 cases in which autopsies were made the oculomotor nerves were affected ten times in 6 cases bilaterally In 100 cases he observed clinically the third nerve was affected thirty four times the sixth nerve was affected sixteen times and the fourth nerve five times We can understand easily why the third nerve is paralyzed so frequently by direct involvement in the gummatous material of the nerve or its roots of origin at the side of the crus

But are there any anatomical conditions which will serve to explain why the paralyses are so often only partial? The nuclei of origin of the rootlets which together make up the third nerve form a series which extends from the posterior end of the third ventricle behind the anterior colliculi to beyond the posterior colliculi The ganglion cells forming these nuclei are of two kinds small and large the former innervate the internal muscles the latter the external muscles of the eyeball There are separate cell groups for each muscle and the levator of the upper lid which so frequently is paralyzed alone is the most anterior group the next being the sphincter pupillæ If then these nuclei have a separate vascular supply or if certain groups have a separate vascular supply we can understand easily how arterial occlusion can bring about a permanent ocular paralysis of one group Now the third nerve nucleus is supplied from two distinct sources an anterior from the posterior cerebral artery and a posterior direct from the basilar artery Those arteries supplying the third nucleus are terminal that is to say their branches do not anastomose with others consequently we can understand how occlusion of one of these two main arteries of supply may produce a paralysis of the levator of the eyelid sparing all the other extrinsic muscles or the converse may occur Furthermore the arteries supplying the groups of nuclei as they ascend vertically from the ventral to the dorsal side give off separate arterial twigs to the separate groups of cells from which arise fibers innervating the several muscles consequently temporary occlusion and complete blocking will lead to a temporary or permanent paralysis of one muscle

Knies asserts that in three fourths of the cases of syphilitic ocular palsies it is the third nerve that is affected Total oculomotor paralysis is much rarer than partial palsies Alexander found 19 cases of total paralysis and 145 cases of partial paralysis Complete oculomotor paralysis without any other disturbance of the cranial nerves and only with general cerebral phenomena is rare

An oculomotor paralysis usually complete of one side with paralysis of face arms and leg of the other side points either to a gummatous process or to a softening of one crus cerebri involving the third nerve and the pyramidal system of the crus producing thereby an alternate hemiplegia

The results of autopsies show that a gummatous mass may involve the stem of the third nerve and only cause either an external or an internal ophthalmoplegia Cases have been described of perineuritis of single intraorbital branches of the third nerve Also a gummatous process in the orbital fissure may cause paralysis of all the external and internal eye muscles anesthesia in the first divisions of the fifth exophthalmos and œdema of the upper eyelid (Nonne)

Fourth and Sixth Nerve Affections Uhtoff found the abducens nerve three times affected in 17 of his own post mortem examinations and in 150 collected cases he found it in 27 of which 6 only were affected bilaterally The causes of affection of the sixth nerve are softening of the pons produced by specific arterial affections gummatous tumors basal meningitis and neuritis

Intrapontine affection of the sixth nerve often is associated with facial paralysis or contralateral paralysis of the extremities Uhtoff found that among 150 collected cases the fourth nerve was affected in six instances and then always in association with other cranial nerves The paralyses of the ocular muscles are of great interest and importance in relation to neurosyphilis and will be considered further in discussing the question of diagnosis

Fifth Nerve Affections According to Uhtoff's statistics the fifth nerve is involved in about 14 per cent of all cases of cerebral syphilis It is affected alone very rarely only four times in 37 cases Generally it is associated with affection of the optic nerves or the nerves of the ocular muscles the affection nearly always is unilateral but a few cases have been recorded in which it has been affected on both sides Hutchinson described two such cases

The sensory portion of the nerve is affected more frequently than the motor in fact only a very few isolated cases have been recorded of paralysis of the muscles of mastication with atrophy Gummata about the base of the brain or gummatous meningitis or syphilitic disease of the base of the skull may affect the Gasserian ganglion or any of all the three divisions of the nerve obviously a basal meningitis may involve the trunk of nerve fibers proceeding from the ganglion to the side of the pons Within the pons the fibers spread out like a fan to end in the sensory nucleus consequently softenings from arterial disease may

produce lesions of these systems of fibers in conjunction with other structures

The disturbances arising from lesions of the fifth nerve may take the form of irritation phenomena in one in several or in all of the branches of the trigeminus and the patient in consequence complains of neuralgic pains in the forehead cheeks temples eye upper jaw lower jaw tongue etc With these pains is associated a hyperesthesia corresponding to the distribution of one or more or all of the divisions of the nerve which sooner or later leads to hypesthesia or even a complete anesthesia Sometimes there is analgesia or hypalgesia The corneal reflex may be abolished and if the gummatous process involves the Gasserian ganglion or the ophthalmic division a neuroparalytic keratitis may occur which in some instances has led to the necessity of enucleation of the eyeball Anosmia due to an affection of the mucous membrane of the nose may follow lesions of this nerve A loss of taste in the corresponding side of the tongue may occur Disease of the fifth nerve often is associated with paralysis of the opposite side of the body

Seventh Nerve Affections The acoustic or eighth is often involved with the facial nerve and may be affected on one side or on both sides The nuclei and roots of origin of these nerves may be involved as well as any part of their course from the base of the brain to their exit from the skull There may result peripheral facial paralysis or deafness or the two may be combined These paralyses may arise in any of the stages of syphilis but they occur most frequently in the earlier periods after infection their pathology is not always identical They may be associated with tertiary lesions gumma of the nerves exostosis of the internal ear basal meningitis neuritis or perineuritis Syphilitic bone disease is also a cause of facial paralysis and deafness with giddiness The prognosis for hearing is unfavorable as a general rule the facial paralysis is transitory but the deafness is irremediable

Eighth Nerve Affections The auditory divisions may be affected separately from the vestibular division in the former case deafness partial or complete or disturbances of hearing may arise in consequence or if the vestibular portion be affected symptoms of Meniere s syndrome may appear

Ninth Tenth Eleventh and Twelfth Nerve Affections Isolated paralyses of the glossopharyngeal or ninth nerve probably would not be recognized but the vagus nerve and its nucleus may be affected and the symptoms noted have been mainly disturbances of the circulation and respiration Especially characteristic is a rapid change of the pulse it may be slow quick or irregular again various respiratory disturbances

towards the end of life are referred to affections of this nerve The spinal accessory either alone or associated with the hypoglossal is affected not infrequently causing paralysis of a vocal cord and soft palate associated sometimes with a paralysis of the trapezius

Meningitis of the Convexity

There are two forms of meningitis of the convexity (a) circumscribed and (b) diffuse The process may start in the bone or in the meninges and spread thence to the brain causing a meningoencephalitis In a few cases the condition has followed a blow on the head which has set up an inflammation either in the bone or in the subjacent dura mater at a definite spot Besides the symptoms already described there is a definite severe headache localized to some particular part of the cranium and a tenderness on pressure or percussion over the spot The general symptoms of tumor or of meningitis may be present if there is a definite tumor formation sooner or later it will cause increased intracranial pressure and the general symptoms of neoplasm will supervene viz vomiting papillœdema slow pulse vertigo and stupor In addition there may be symptoms pointing to the local situation of the lesion according to the region of the cortex in which it is situated If situated in or near the motor area it may give rise to epileptiform attacks (Jacksonian epilepsy) and monoplegia or hemiplegia It has been asserted that when Jacksonian epilepsy occurs we have a certain indication of the seat of the tumor and it is important to discuss this question for experience has shown that a gummatous tumor which has developed in the substance of the brain cannot be resolved by antisyphilitic remedies to the same extent as if it were limited to the meninges Mott saw quite a number of cases of this kind associated with epilepsy or migrainous attacks some of which had been treated for a long time with antisyphilitic remedies without relief and which on post mortem examination showed a cortical gummatous tumor or tumors He concluded that it was probable that absorption of the necrobiotic material in the brain could not be accomplished in the same way as with a superficial gumma of the bone or skin

The gummatous tumor or syphilitic pachymeningitis may be situated in other regions of the brain and give definite localizing symptoms Thus homonymous hemianopia partial or complete may arise from a gumma in the occipital lobe involving the optic radiations or calcarine region A gummatous tumor in the left hemisphere if deeply seated may cause a motor aphasia word blindness when situated at the angular gyrus or word deafness if situated in the posterior third of the first temporal and

the adjacent gyri of Heschl when Broca s convolution is involved there is motor aphasia or dysarthria difficulty of articulation usually accompanied by facio lingual palsy In a case of Wernicke s a bilateral gummatous lesion produced deafness Gummatous tumors anywhere in the speech zone may by involving the association fibers of the various speech centers produce paraphasic and amnesic conditions Likewise lesions of the parietal lobe have caused apraxia and parapraxia

Charcot considered cortical epilepsy to be one of the commonest results of cerebral syphilis but Naunyn found only 3 per cent in over 300 collected cases Without a post mortem examination statistics are not very reliable and should the autopsy be made some long time after the onset of the disease regressive changes may have occurred to such an extent that although the fits at first localized have been followed by general convulsions indistinguishable from epilepsy little is left behind to show the original meningitis which gave rise to the initial symptoms

Arteritis

Meningitis whether in the diffuse form or in the form of a localized gummatous tumor is always associated with some degree of endarteritis The symptoms of meningitis usually precede those of arteritis but they may be simultaneous or even successive In the cases occurring within the first two years after infection the morbid process often is more extensive and widespread than the symptoms indicate Cases occur however in which the symptoms of arteritis precede any symptoms of meningitis and in fact are independent of any signs of meningitis either at the time or subsequently Symptoms of arteritis may occur at almost any period after infection The earliest case independent of any signs of meningitis seen by Mott was the following

A commercial traveller aged 38 who six months after infection while seated at the piano singing a comic song to his own accompaniment suddenly became faint and speechless His friends at first were amused and did not realize that it was not a part of the entertainment They then came to his help and gave him a glass of water which he was unable to swallow the fluid regurgitating through the nose This was followed the next day by paralysis of the left leg left arm and left side of the face including the upper part and for a month he had to be fed with a tube This happened in Japan the doctor treated him by inunction and after a month he was able to swallow and speak He was seen by Mott on his return from Japan suffering with the remains of a left sided paralysis including the upper facial muscles and there was also paresis of the left

towards the end of life are referred to affections of this nerve The spinal accessory either alone or associated with the hypoglossal is affected not infrequently causing paralysis of a vocal cord and soft palate associated sometimes with a paralysis of the trapezius

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Psychical symptoms may be manifested by mental fatigue and incapacity for work associated with abnormal excitability sometimes there is an incapacity of power of thinking and an enfeeblement of intelligence or a general obtuseness associated with an emotionality and tendency to cry The patient often exhibits a semisomnolent half intoxicated condition with a lack of power of recalling afterwards what has happened Periods of excitement may alternate with conditions of apathy and longer or shorter periods of somnolence may occur in which the patient performs actions in a semiautomatic manner As already mentioned in the description of basal meningitis these semisomnolent semiconscious conditions are especially suggestive of a widespread endarteritis producing cerebral anemia and although regressions even to the patient recovering consciousness in almost a complete manner may occur their presence indicates a doubtful prognosis A drowsy sleepy condition is an early symptom especially noticed by the wife or friends of the patient This accords with other symptoms which at first are transitory but eventually become more persistent The transitory character of the earlier phenomena before the occurrence of thrombosis is a very important feature of the disease It can be easily understood that if one or more of the large arteries be partially occluded considerable variations of the blood supply and blood pressure in the hemispheres may result and this accounts for fainting fits and loss of consciousness mistakable for a true apoplectic seizure of general paralysis The onset of symptoms may be quite sudden and without any of the prodromal symptoms previously mentioned moreover there is not necessarily a loss of consciousness especially when hemiplegia comes on gradually There is no loss of consciousness when the clotting in the vessel is gradual or when the blocking of the vessel does not interfere seriously with the cortical functions But various conditions of apoplectic seizure may occur varying from slight disturbances of consciousness giddiness nausea and stupefaction to complete loss of consciousness and in some cases associated with convulsions Apoplectic seizures may occur during sleep they may follow excesses in baccho et venere or physical or bodily strain These seizures present no essential difference from the apoplectic seizures met with in other diseases except that they occur frequently from syphilis in young male adults between twenty and thirty five an age in which hemorrhage or thrombosis of the vessels from other causes is rare Of course exception should be made to valvular disease of the heart and subsequent embolism A characteristic of the seizure is that if a slight one the defect is of a transitory character One of the earliest symptoms as Charcot pointed out is a transitory aphasia sometimes it is loss of memory of words but there may be any

vocal cord and soft palate He was seen for some years without further symptoms and gradually improved This case illustrates that an attack caused by occlusion of a blood vessel may occur independently of any previous meningitic symptoms

About one fourth of the cases of arteritis with clinical symptoms occur within the first two or three years It is right to emphasize clinical symptoms because a number of cases doubtless occur in which there may be some slight and overlooked meningitis or arteritis but not sufficiently extensive or intense as to give rise to symptoms which will bring the patient under observation The symptoms of arteritis may be due to general thickening of the intima causing occlusion or partial occlusion of the vessels and interfering with their contraction and dilatation both by the change in the muscular coat as well as by the effect of the disease on the vasomotor nerves but as a rule the obtrusive signs which terminate in actual localized loss of function are due more often to thrombosis of a diseased vessel There is no time limit to the possibility of symptoms arising from endarteritis the result of syphilitic infection still as a rule however it is in young male adults within the first few years after infection that thrombosis occurs and it may be associated with signs of meningitis Arteritis may manifest itself first by an apoplectic attack and preceding this various prodromal symptoms often occur namely headache giddiness sleeplessness and various psychical changes in the form of irritability of temper incapacity for mental work lack of decision of character weakness of memory especially for recent events slowness of thought and weakness of ideation

Symptomatology — *Headache* is not so severe as in meningitis and it may exist for months before other symptoms arise It is rarely localized and although often worse at night, it is difficult to differentiate from the headache of arteriosclerosis in later periods of life It may be intermittent and then usually it is more severe while it lasts which may be weeks or months it may then disappear for a time again to reappear usually it is increased by mental activity and sometimes even by bodily effort

Vertigo The patient may be subject to short attacks of giddiness they may last for weeks or months and be the sole obtrusive symptom of which the patient complains If the patient lying on the back, be made suddenly to assume the erect posture a feeling of giddiness and faintness may be experienced owing to the inability of the diseased vessels to readjust the circulation in accordance with the necessity of altered gravitation caused by the sudden change of position

Sleeplessness may be transitory or chronic or the sleep may be restless the patient waking in the morning unrefreshed

patches of softening involving important cranial nuclei and the motor and sensory tracts on one or both sides The same applies to the crus cerebri a softening there causes an alternate hemiplegia characterized by paralysis of the motor oculi on one side with paralysis of the face arm and leg of the other When the softening is in the pons or medulla it may involve the nuclei of important cranial nerves and the symptoms arising therefrom may be associated with a hemiplegia on one side due to the involvement of the pyramidal system before it has decussated associated with a paralysis of a cranial nerve If the facial nucleus is involved in association with the pyramidal system of the arm and leg before it has decussated an alternate hemiplegia occurs It differs from an ordinary cerebral hemiplegia by the fact that there is paralysis of the upper face muscles and reaction of degeneration and the facial paralysis is on the opposite side to the paralysis of the arm and leg Alternate hemiplegia does not always result in syphilis from a softening of the pons as the following case shows A patient came under observation suffering from alternate hemiplegia He had a left peripheral facial paralysis which had been preceded by an attack of right hemiplegia It was shown at the autopsy that a gumma of the facial nerve was the sole cause of the facial paralysis and a softening in the internal capsule of the left side was a cause of the right hemiplegia

Aneurysm may result from endarteritis The patient may suffer from several slight faints and then suddenly suffer with an apoplectic seizure and die Such a case of medicolegal interest is the following A workman who had suffered with several faints was working on a roof and fell down but without injury to the body He developed a slight hemiplegia and aphasia Three months later while sitting up in bed he was seized with an apoplectic stroke and he died in less than an hour On post mortem examination an aneurysm of the left middle cerebral as large as a small chestnut was found There was old obliterative endarteritis which had given rise to the aneurysm and its rupture had caused sudden death

Diffuse Cerebrospinal Meningitis

Most of the cases of basal syphilitic meningitis examined post mortem have shown that the inflammation has extended to the spinal cord but owing to the intensity of the cerebral symptoms any spinal manifestations were overshadowed or the patient was not in a fit state to express his subjective feelings and thus afford the necessary proof of their existence

Again when we speak of spinal meningomyelitis even when the lesions

form of speech defect This transitory trouble of speech may occur several times in the day or there may be transitory astereognosis asymboly apraxia word blindness word deafness or other forms of disordered vision or hearing A paraphasia is perhaps the most frequent of the speech troubles met with Again a transitory monoplegia hemiplegia or hemiparesis ushered in by numbness or tingling of the part may be an early symptom The paresis or paralysis may last a few minutes a few hours or a few days and then may disappear again to return and eventually end in a permanent loss of function and contracture In some cases there is a hemiplegia gradatim that is to say the paralysis gradually spreads over one side of the body A monoplegia or this gradual mode of onset of hemiplegia suggests a cortical lesion The patient sometimes can describe exactly the onset of the paralysis or aphasia but usually at the time that it occurred there was giddiness dullness of perception or somnolence and these symptoms persist sometimes after the paralysis has passed off It is much more common to find loss of motor power than loss of sensibility but various sensory phenomena may occur such as pain numbness and tingling in the limbs partial hemianesthesia and hemianopia

Homonymous hemianopia may arise from occlusion of a posterior cerebral artery causing softening of the optic radiations and calcarine region of the occipital lobe

Syphilitic endarteritis of the lenticulo striate arteries may cause patches of softening of variable size in the basal ganglia corpus striatum thalamus and internal capsule The most varied symptoms may arise therefrom in the form of hemiplegia triplegia hemiplegia of one side with hemiparesis of the opposite side Occasionally when the damage is in the anterior third of the posterior segment of the internal capsule on both sides a condition of pseudobulbar paralysis occurs Emotional disturbances the patient being easily moved to tears or laughter are especially significant of softening of the basal ganglia Sometimes the thalamic syndrome of Roussy may be present viz contralateral hemianesthesia and hemianalgesia with pain in the anesthetic region mild hemiparesis hemiataxia and athetoid movements

The most serious symptoms arise when occlusion of the basilar artery occurs such a condition is fatal almost invariably Mott made an autopsy on a woman past middle life who having become suddenly unconscious developed Cheyne Stokes breathing and died two hours later He found an endarteritis of the basilar artery with recent extending thrombotic occlusion Sometimes a partial obliterative endarteritis may affect this vessel and extend into some of the terminal arteries causing

patches of softening involving important cranial nuclei and the motor and sensory tracts on one or both sides The same applies to the crus cerebri a softening there causes an alternate hemiplegia characterized by paralysis of the motor oculi on one side with paralysis of the face arm and leg of the other When the softening is in the pons or medulla it may involve the nuclei of important cranial nerves and the symptoms arising therefrom may be associated with a hemiplegia on one side due to the involvement of the pyramidal system before it has decussated associated with a paralysis of a cranial nerve If the facial nucleus is involved in association with the pyramidal system of the arm and leg before it has decussated an alternate hemiplegia occurs It differs from an ordinary cerebral hemiplegia by the fact that there is paralysis of the upper face muscles and reaction of degeneration and the facial paralysis is on the opposite side to the paralysis of the arm and leg Alternate hemiplegia does not always result in syphilis from a softening of the pons as the following case shows A patient came under observation suffering from alternate hemiplegia He had a left peripheral facial paralysis which had been preceded by an attack of right hemiplegia It was shown at the autopsy that a gumma of the facial nerve was the sole cause of the facial paralysis and a softening in the internal capsule of the left side was a cause of the right hemiplegia

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Again when we speak of spinal meningomyelitis even when the lesions

point to a focal spinal lesion a careful examination and consideration of the symptoms afforded by a reliable history often will show some evidence of basal meningitis There is in fact a generalized infection although the inflammatory reaction may be sufficiently intense in only one region to give rise to definite symptoms

There are certain symptoms however which indicate diffuse cerebrospinal meningitis In addition to the symptoms of basal meningitis already described the following spinal symptoms occur pain and stiffness in the back paresthesia e g pins and needles numbness in the limbs and radiating pains owing to inflammation of the posterior roots girdle sensation hyperesthesia of the skin and occasionally an atrophic paralysis due to involvement of the anterior roots

A stuporose condition of the patient may render it difficult to find out these spinal symptoms Loss of control of the sphincters may be due either to the cerebral or spinal condition Pyrexia is either absent or anomalous in character The cerebrospinal fluid contains abundance of lymphocytes and gives a positive Wassermann reaction

Prognosis in Syphilis of the Brain

The prognosis of cerebral syphilis depends upon many factors and may be discussed in various ways The first question that arises is whether a well marked and typical Hunterian chancre is more likely to be followed by serious syphilis of the central nervous system than a primary manifestation of less typical character Now there are two points to be considered in coming to a correct conclusion the first being the question whether the difference in the local sore at the point of inoculation is due to the virus in one case being more active than in the other or whether the reaction of the individual is different It is possible that the person with a typical Hunterian chancre would if untreated suffer with more serious secondary and tertiary sequelæ including disease of the nervous system but the severity of the local manifestation leaves no doubt in the mind of the patient and practitioner that energetic treatment is called for and must be continued for several years in the second case of atypical primary sore there are doubts in the mind of the patient as to its being anything serious and he neglects altogether to attend a doctor until symptoms arise or sometimes he may be unfortunate enough to seek advice from a medical man who still thinks there is only one form of syphilitic sore the hard chancre and he advises only local treatment This accounts in a measure no doubt for the fact that severe syphilitic disease of the nervous system occurs as frequently in

mild primary and secondary affections as in the more severe forms and serves to emphasize the fact that the diagnosis of primary syphilis is no longer a clinical but a laboratory problem in the dark field identification of the spirochete

There can be no question of the beneficial influence of early treatment and all writers are agreed upon this point Fournier Lang Oppenheim Hjellmann Nonne and others held that nervous affections were more likely to occur when antisyphilitic treatment had either been insufficient or not practised at all Many of the more severe cases have had no treatment prior to coming under observation and care The most responsive to treatment are cases of meningitis cerebral spinal or cerebrospinal provided the symptoms point to irritation rather than paralysis if there be associated monoplegia or hemiplegia aphasia apraxia alexia or hemianopia even though these conditions be transitory the prognosis is more serious for they indicate arterial disease which is less susceptible to treatment than meningitis A basal meningitis with paralysis of one or more of the cranial nerves will yield to treatment by arsphenamine and mercury or bismuth if the optic chiasma and optic nerves are involved there is a danger of postneuritic atrophy followed by partial or total blindness This condition of basal gummatous meningitis however is not so serious if it be treated early before the arteries are affected by endarteritis Treatment should produce a rapid improvement of the symptoms and if at the end of three or four weeks there are no signs of benefit it is improbable that much improvement can be hoped for The cases of cerebral syphilis with mental symptoms fits lapses of consciousness and drowsy stupor are generally more serious improvement may occur but complete recovery is rare some cases often proceed from bad to worse in spite of treatment and sooner or later terminate fatally sometimes after several remissions

The most unfavorable cases are those which simulate general paralysis for a widespread affection of the brain is indicated cases of softening from arterial occlusion are not very favorable endarteritis being one of the most serious and the most insidious of all forms of cerebral syphilis advanced disease may occur without producing any very definite symptoms perhaps persistent headache only perhaps transitory aphasia monoplegias or hemiplegias following a faint or a fit If such a case be treated early the prognosis is much better than later when the loss of function has become permanent for this denotes tissue necrosis and little good can be done towards curing a hemiplegia when contracture has occurred Too often a favorable prognosis is given in such cases because it is of syphilitic origin owing to a lack of understanding of the patholog

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may be sudden death from apoplexy due to rupture of a cerebral vessel or thrombosis of the basilar artery.

When a patient is found to be suffering with serious organic disease of the nervous system the hope of the physician is that the disease may turn out to be neurosyphilis and not tubercle or malignant tumor for experience has taught him that the administration of antisyphilitic remedies in what appears to be a hopeless condition sometimes may be followed by amelioration, cure or partial cure.

Symptomatology of Syphilis of the Spinal Cord

The symptoms of syphilis of the spinal cord may be localized or general; they depend essentially upon the effects of (a) the meningitis causing irritative and destructive changes in the roots localized or generalized; (b) the extension of the inflammation along the pial septa into the substance of the cord with subsequent cicatricial formation leading to destructive changes in conducting paths to and from the brain; (c) the changes in the vessels, arteries, veins and lymphatics causing ischemia and softening of the nervous structures local or generalized by obliterative endarteritis, endophlebitis, congestive stasis and thrombosis.

The clinical forms depend upon the degree and intensity of one or other of these processes operating singly or in combination with another or both. As in cerebral syphilis polymorphism is a characteristic feature; at one time the symptoms may point to meningitis and at a later period to myelitis. It is well to remember that the pathological changes in the meninges are more marked than the gravity of the symptoms would indicate; in fact grave symptoms may come on only when a local or generalized myelitis has occurred. It cannot be emphasized too strongly that the more serious organic changes occurring in the spinal cord as in the brain result essentially from vascular disease, especially when a spreading thrombosis due to arteritis takes place.

The spinal dura mater may be attacked consecutively to a vertebral caries; it may be the primary seat also of a diffuse or circumscribed gummatous infiltration. This may be localized to one part of the cord causing a localized pachymeningitis, or it may be diffuse. Not infrequently the *affection of the dura mater may take the form of a gummatous tumor* or it may lead to an affection in one region of the cord, e.g. the cervical frequently is the seat of the disease causing hypertrophic pachymeningitis.

Gummatous tumors situated in the dura mater and compressing but not infiltrating the spinal roots and spinal cord are comparatively rare and only a few such cases have been described. It is much more common

ical process Nervous tissue once destroyed cannot be replaced Many cases show that cerebral syphilis follows a head injury These cases generally respond well to treatment probably the injury causes a local node or gumma

Pure basal meningitis does not indicate a bad prognosis neither does involvement of a cranial nerve e g the motor oculi rather the reverse for it brings a patient early under treatment Marked papillœdema may disappear and restoration of sight may be complete or almost so under treatment Progressive optic atrophy generally ends in blindness

Basal meningitis is much more favorable when limited to one side frequently however it is associated with arteritis the prognosis then is bad because occlusion of arteries at the base of the brain may occur and a very small patch of softening in the pons or medulla may lead to serious paralysis and fatal complications Acute bulbar symptoms always are serious but when they occur in the secondary stage vigorous anti syphilitic treatment sometimes may be followed by very satisfactory esults

Some of the most successful cases are those of apparent local gum matous pachymeningitis the result of a head injury and cases in which there were no symptoms pointing to loss of function only headache localized pain and tenderness and cortical irritation causing Jacksonian epilepsy Pseudobulbar symptoms always are serious as they imply that both hemispheres are affected and they indicate a widespread arterial affection with bilateral capsular or cortical softening

When the infective process has subsided in one situation under the influence of treatment occasionally it may arise in another situation probably owing to a colonization Therefore a guarded prognosis should be given always in all cases of neurosyphilis According to Naunyn only after five years complete freedom from symptoms can it be asserted that a cure has been effected without any likelihood of further symptoms arising When we have reason to suppose that the disease is a localized pachymeningitis and the symptoms disappear we can give usually a favorable prognosis The examination of the cerebrospinal fluid for lymphocytes and protein content as well as the Wassermann reaction in fluid and blood may assist in giving a prognosis while it may also afford information as to the influence of treatment The lymphocytes may dis appear entirely from the cerebrospinal fluid for a time under the influence of treatment and then there may be a reappearance very likely it will be shown that this corresponds with a fresh colonization of the organism

A progressive dementia and attacks of drowsy stupor indicate exten sive disease and the prognosis always is very grave Occasionally there

ciated with areas of paresthesia or hyperesthesia in which pains and a diffuse painful sensibility on pressure may occur Among the most common and significant sensory troubles is the girdle pain According to Charcot these pains are worse at night in many cases however the pains may be so slight as to be overlooked These subjective symptoms of root irritation are of great diagnostic importance as they constitute the earliest symptoms of the disease Under the influence of energetic treatment a rapid improvement generally occurs Besides these subjective symptoms indications of sensory root irritation there may be symptoms and signs of motor root irritation in the form of spasm and cramps of muscles In many cases there is stiffness of the spine combined with some general tenderness on percussion as well as pain on assuming the erect posture The superficial and deep reflexes are increased at first If the roots are seriously involved by gummatous infiltration actual destruction of fibers may occur giving rise to patches of anesthesia and analgesia Such a group of symptoms pointing indubitably to meningitis usually is unaccompanied by pyrexia

Severe paralysis with muscular atrophy and change of electrical excitability indicates a severe affection of the motor roots with destructive atrophy

In addition to symptoms already mentioned are others characteristic of meningitis viz regional hyperesthesia and anesthesia vasomotor changes and irritative phenomena in nearly all cases there is more or less trouble with the bladder in addition there is some paresis of the limbs or of a single extremity not infrequently the patient does not move a limb on account of the fear of movement exciting painful paroxysms and it may be thought that the limb is paralyzed Although doubtless cases of pure syphilitic spinal meningitis do occur the opportunity of verifying this post mortem seldom if ever occurs for the disease all the while it remains limited to the membranes of the spinal cord and has not extended to the cord itself or affected the vessels so seriously as to cause occlusion is not fatal and usually yields readily to treatment As already mentioned syphilitic meningitis is an early often a very early symptom of neurosyphilis

Oppenheim has laid stress upon the variability of the condition of the knee jerks one day they may be brisk and after a few days disappear again to reappear This may be explained by the fact that the intensity of the inflammatory process tends to subside in one situation while extending to another Thus the roots which are connected with the reflex arc on one occasion may not be affected and a little later they are seriously involved or vice versa The tendency of meningitis is however to extend to the

for the whole of the membranes to be involved and probably the process starts usually in the soft membranes and spreads to the dura on the one side and to the spinal cord and roots on the other causing a meningomedullary adhesion This pachymeningitis may be focal and take the form of a ring around the cord or it may occur in widespread patches

Gumma of the spinal cord is rare Cases have been described by Williamson and Gowers the tumor being situated in the posterior horn by Eisenlohr in the posterior column and by Osler in the anterolateral column and in different cord roots The gumma practically always is associated with other lesions macroscopic or microscopic e g diffuse meningitis pachymeningitis and arteritis

The medullary or meningomedullary gumma may be solitary or multiple it is variable in size and usually starts in the membranes or in the roots but it may arise in the substance of the cord The naked eye and microscopic characters are the same as those of gumma in the brain it may cause secondary degeneration in systems of fibers in the spinal cord and when situated in the lateral column it has given rise to the characteristic Brown Sequard phenomenon

The symptoms which may be presented by spinal syphilis of necessity must vary according to the extent and intensity of the chronic inflammatory process The lesion may be localized or generalized throughout the spinal canal or there may be scattered foci of the disease The symptoms of the disease will depend upon the roots and segments of the cord that are involved and damaged by the gummatous infiltration and particularly by its spreading along the septa to the substance of the cord involving thereby the long conducting tracts of fibers to and from the brain in such case a focal meningomyelitis leads to the symptoms of a transverse focal myelitis Although the symptoms vary in different individual cases yet certain signs and symptoms and the peculiarities of their onset and progress are fairly constant and of characteristic significance and diagnostic importance

Spinal Meningitis

The inflammation of the membranes is manifested by a feeling of stiffness in the neck and the back by Kernig s sign by pains in the neck the back and the sacrum not infrequently severe and obstinate but sometimes only of moderate severity and unaccompanied by hyperesthesia numbness tingling pins and needles or severe pains radiating into the upper and lower limbs or in various parts of the trunk may occur asso

pains and perhaps atrophy of some muscles of the arms. When the lowest cervical and first dorsal segments are affected we may have affection of the sympathetic contraction of the pupil, enophthalmos and perhaps one half of the face shows anidrosis or dysidrosis, anomalous secretory activity of the sweat glands. Cervical meningomyelitis often is associated with some evidence of preexisting basal meningitis. If the lumbosacral region is the seat of the meningomyelitis there is a possibility of a flaccid paralysis of the legs, and superficial as well as deep reflexes will be abolished; moreover the sensory disturbance will be severe in the lower extremities.

But the most serious symptoms relate to the bowel, the bladder and the genital organs. There may be incontinence of feces and of urine although the bladder is never empty. The detrusor and sphincter both may be paralyzed, and urine dribbles away continuously from a paralyzed distended bladder. Such a condition sooner or later ends in cystitis, which is difficult to treat and is liable to be followed by pyelonephritis.

Again, partly owing to the difficulty of keeping the patient clean and the skin aseptic, and partly to the vasomotor and trophic disturbances, sacral bedsores are very liable to arise. Impotence in the male may arise as a result of the roots and spinal centers connected with the genital act being involved in the morbid process.

Other varieties of meningomyelitis, e.g., spinal hemiparaplegia with crossed hemianesthesia (Brown-Séquard syndrome), may occur. Armstrong has reported a case of crural monoplegia accompanied by anesthesia of the opposite limb arising two years after the chancre. It was cured by treatment. Brown-Séquard's syndrome rarely occurs except in syphilis of the spinal cord. It is rare for syphilis to cause paralysis of all four limbs. Cases have, however, been recorded by Weidner and Buttersack. Usually a transitory weakness of the upper limbs, accompanied by a certain amount of rigidity, is all that is found. Certain muscular atrophies of a progressive type resembling progressive muscular atrophy have been described as complications of syphilis (syphilitic amyotrophy).

Gummatous Meningitis of the Cauda Equina

A gummatous meningitis may affect the structures in the lower end of the spinal canal, causing a complex group of symptoms due to irritation and loss of function of the roots of the cauda on one or both sides; not infrequently the symptomatology points to a unilateral affection.

Spiller has described also an affection of the conus medullaris in cerebrospinal syphilis.

spinal cord and produce the commonest form of spinal syphilis meningo myelitis

Cases in which the pains are very severe and paroxysmal and in which there are stiffness and rigidity are more favorable for they indicate that the roots are irritated but that the disease has not made enough intramedullary extension to interfere with the transmission of sensation to the brain and usually such cases yield to treatment

Meningomyelitis

The meningitic symptoms often precede by days weeks and months the symptoms of a focal myelitis and fortunately may be so severe as to cause sufficient alarm in the patient to make him consult a doctor in other cases they may be so trifling that the patient puts down to muscular rheumatism the stiffness in the back and the radiating pains in the limbs until a girdle sensation with paresthesia and paresis in one or both legs leads the patient to consult a doctor or perhaps no advice is sought until the motor weakness has increased to a paraplegia The paresis or paralysis is mostly of a spastic character The disturbances of sensibility may be those of meningitic affection of roots already described combined with those due to an imperfect transverse lesion

There is often sensory dissociation thus the temperature sense may be affected whilst the light tactile pressure sensations and the prick of a pin may be felt and correctly localized or just the converse may be the case

The deep reflexes are increased at an early stage the abdominal reflexes may be normal diminished or absent One of the earliest most important and most persistent of symptoms is some bladder trouble and for this the patient often consults a doctor the other signs and symptoms being discovered upon examination Andre Thomas has called attention to the premonitory period of syphilitic paraplegia He asserts that one of the principal signs is intermittent spasm of vessels of the spinal cord The symptoms are diffuse motile and transitory they appear and disappear suddenly Unusual sensations giving way of the legs spinal pain and bladder troubles are among the transitory complications If we recognize this premonitory period and institute early antisyphilitic treatment the patient may be saved from an irremediable infirmity

The most frequent seat of meningomyelitis is the dorsal region with symptoms of a transverse focal myelitis viz spastic paraplegia and loss of control or impairment of sphincters When the cervical region is affected a paresis of all four limbs may occur associated with radiating

complete loss of movement The segmental level of the spinal lesion determines the extent of the motor paralysis of the trunk it is extremely rare for the upper extremities to be affected and few such cases have been reported

In the majority of cases there is a profound sensory affection although individual cases may exhibit various forms of disturbance of sensory function in some cases there is a complete loss of sensibility to all forms of stimuli or there may be a retention to a more or less extent of certain sensations while others are lost the appreciation of thermal sense is especially likely to be retained when the others are abolished but it may happen that light tactile sensation is retained although there may be analgesia and thermoanesthesia even thermoanalgesia may alone constitute a sensory disturbance

A Brown Séquard syndrome may occur occasionally The tendon reflexes are lost when the myelitis affects the lumbar spinal cord if however it affects only the dorsal cord the tendon reflexes may be present and even exaggerated

The sphincters of the bladder and rectum are affected early and severely and œdema due to a vasomotor paralysis is especially liable to occur in the paralyzed lower extremities moreover large rapidly spreading bedsores over the sacrum occur early and often lead to septicemia and a rapidly fatal termination

Prodromal Symptoms Sensory paresthesia and radiating shooting and stabbing pains may be felt in the lower extremities in the hips and in various parts of the trunk and spine Besides there is often a certain stiffness of the back and spinal irritation Motor irritation is manifested by spasmodic contractions and cramps in the lower limbs the feet and the toes alternating with a feeling of weakness and followed by paretic conditions The bladder and rectal symptoms are manifested first by retention and constipation but later there is incontinence of urine and feces

The patellar reflex may vary between excessive normal and diminished activity These prodromal symptoms may last days weeks or occasionally even months The temporary character of the prodromal symptoms appearing suddenly or comparatively suddenly and after a varying period of time has elapsed disappearing again to reappear and sooner or later ending in a definite spinal paralysis is especially suggestive of syphilitic myelitis In such a case the application of the Wassermann reaction to the blood and cerebrospinal fluid in the early prodromal stage is essential for diagnostic purposes

In the fully established form of the disease a marked improvement

Erb's Spastic Spinal Paralysis

Erb in 1892 described a group of cases occurring in the subjects of syphilis which he considers are distinct from focal meningomyelitis in the dorsal region and due to a primary degeneration in the ascending cerebellar and posterior median tracts and the crossed pyramidal tracts The symptoms occur later and there develops gradually a spastic paresis of the legs with marked increased deep reflexes although the gait is extremely spastic the muscular contraction is but slight The bladder is early and almost constantly affected Disturbances of sensibility usually are present but only slightly manifest The course is chronic in most cases and there is a tendency to improvement to remissions and even to complete arrest The disease may extend over many years and the danger to life is only by complications intercurrent disease and especially cystitis and septic infection or from the occurrence of other disease of syphilitic origin

When in 1892 Erb published his description of the disease no post mortem evidence thereon was forthcoming He regarded the probable anatomical basis of the disease as a symmetrical degeneration in the posterolateral columns Numerous neurologists including Oppenheim and Marie asserted that these cases were really due to a syphilitic meningomyelitis Since that time nine or ten cases of typical syphilitic spinal paralysis with post mortem examinations have been published and Nonne believes that although syphilitic spinal paralysis is clinically a well defined entity it has by no means a constant unvarying morbid anatomy

Acute Transverse Myelitis

Acute myelitis may occur in the subject of syphilis Leyden in 1874 reported cases representing the clinical picture of acute myelitis and since then numerous contributions have been made in which the anatomical basis of the affection has been described

Some statistics show that it is a relatively frequent form of syphilitic disease of the spinal cord thus Orlowsky found 19 cases out of 72 Nonne saw it much less frequently viz three times in 92 private cases and five times in 120 hospital cases

It may come on quite acutely the lower limbs being completely paralyzed in a few hours or the development of a complete paraplegia may occur only after a few days The paralysis is almost always total and absolute so that from the pelvis down to the sole of the foot there is

Prognosis in Syphilis of the Spinal Cord

In giving a prognosis the first requirement is to ascertain into which of the following groups we should place the affection from which the patient is suffering (1) coincident nervous diseases (2) meningovascular neurosyphilis (3) parenchymatous neurosyphilis There is no form of nervous or mental disease which may not be coincident with the history of antecedent syphilis and the hope may be reasonably entertained in many cases that antisyphilitic remedies may be followed by beneficial effects and with a varying degree of probability a favorable prognosis may be given according to the likelihood based upon previous experience of the symptoms improving with treatment The more certainly the diagnosis points to active syphilis being the direct cause of the symptoms the more favorable is the prognosis in grave organic disease of the nervous system because provided the symptoms are mainly irritative phenomena such as pains or muscular spasms and stiffness and not paralytic phenomena the more likely are they to clear up with treatment

If the diagnosis therefore points to meningitis in the early stages the prognosis of a perfect recovery is fairly good and if the patient is kept under observation and treatment for some years it is probable that recovery may be permanent the longer the time that elapses without return of symptoms the more favorable is the prognosis of a complete and lasting recovery It is well however to give a guarded prognosis for it is astonishing for how long the spirochete may lie dormant and when the syphilitic infection is almost forgotten the latent virus under some predisposing or exciting cause may resume an active state with the sudden or gradual onset of characteristic clinical symptoms

If the diagnosis points to a generalized syphilitic disease involving the blood vessels and the substance of the brain and spinal cord as well as the membranes with mental and paralytic symptoms the prognosis is grave not only is the patient likely to be permanently affected in body and mind but the disease may prove fatal within a few years Such symptoms indicate widespread destruction of nervous tissue with secondary degeneration and liability to further destruction by thrombotic softening or encephalitis and myelitis conditions causing damage which cannot be restored by antisyphilitic remedies nevertheless it is extraordinary how much improvement may occur sometimes from antisyphilitic treatment in a patient who previously has had either no treatment or only inadequate treatment Meningovascular neurosyphilis such as meningomyelitis localized syphilitic gummata and gummatous pachymen

may occur for days or weeks even without any special therapeutic treatment, but this improvement may not continue and even the symptoms may all return In some cases the disease may run a very rapid course terminating fatally in a short time Thus Williamson has described a case fatal on the sixteenth day and Schmaus a case which died on the fourteenth day

Syphilitic Poliomyelitis or Amyotrophy The anterior horn cells may be affected in the course of a myelitis or meningomyelitis there will then be paralysis accompanied by wasting of group of muscles corresponding to the segments of the spinal cord affected moreover there will be electrical changes and reaction of degeneration The changes which would be found in the spinal cord would correspond to those found in all forms of myelitis in which the anterior cornua are the seat of the inflammation

Pseudotabes Syphilitica

Oppenheim and Eisenlohr simultaneously in 1888 observed cases of individuals the subjects of antecedent syphilis who presented a series of symptoms simulating tabes dorsalis at least in one stage of the disease, symptoms which disappeared or at any rate improved under antisyphilitic treatment moreover anatomical research in fatal cases has demonstrated the existence of a syphilitic meningitis involving the posterior roots with secondary degeneration of the posterior columns Oppenheim has designated this affection as pseudotabes

The main symptoms are absent knee jerks ataxia lancinating pains and bladder troubles Besides in these cases brain symptoms analogous to those of tabes occur viz ocular palsies transitory or permanent pupil rigidity more often than not both to light and accommodation laryngeal paralysis nerve deafness anesthesia in the distribution of the fifth nerve which may be due partly to basal meningitis and gummatous neuritis and partly to simple atrophy of the cranial nerves and their roots

Wilbrand and Saenger state that in a case where there is a history of acquired syphilis followed later by tabetic phenomena the appearance of a central scotoma must not be considered a symptom of commencing optic atrophy but as an expression of a syphilitic retrobulbar neuritis affecting the papillomacular bundle It may therefore be concluded that every case of defective vision with tabetic symptoms is not parenchymatous neurosyphilis but may be due to active syphilis and will therefore respond rapidly to antisyphilitic treatment.

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DIAGNOSIS OF SPINAL AND CEREBROSPINAL SYPHILIS

It is seldom that the spinal cord is the only seat of a syphilitic lesion of the nervous system for if the virus gains access to the subarachnoid space the tendency especially when symptoms arise within a few years of the primary infection is to affect the base of the brain as well as the spinal axis If there be a basal meningitis it is highly probable that there is some degree of coexistent cerebral arteritis which if it does not cause any symptoms of cerebral softening or cranial nerve (nuclear) paralysis at the time of the spinal affection may do so subsequently A patient presenting himself with symptoms pointing to affection of the spinal cord may give a history of antecedent syphilis and yet not necessarily be suffering from syphilitic disease of the spinal cord It is therefore necessary either to prove the existence of a syphilitic affection or exclude it this can be done by inquiry by examination for syphilitic residua and by the Wassermann reaction in the blood and cerebro spinal fluid as well as from other pathological changes in the latter

It must be borne in mind that there is no clinical symptom or group of symptoms characteristic of syphilitic disease of the spinal cord but there are certain symptoms which if they occur in young adults particularly of the male sex should make us suspect their syphilitic origin The early symptoms are due to spinal root irritation viz paresthesia numbness tingling pins and needles or shooting boring pains having a spinal segmental distribution in the trunk or limbs muscle rigidity cramps and contractures of the limbs bladder troubles alterations in the deep reflexes in fact symptoms pointing to a local or more generalized meningitis but usually without pyrexia unless there be some complication causing septic absorption As in cerebral syphilis so in spinal cord disease the symptoms are particularly liable to remissions and regressions One group of symptoms may improve or even disappear and another group appear or symptoms may improve in one part of the body while progressing in another The cerebro spinal fluid may show an increase in the lymphocytes and probably a positive Wassermann reaction thus serving as a means of differentiation from spinal conditions giving rise to similar symptoms e g caries or new growth also a tumor of the spinal cord may cause root irritation and give rise to these subjective symptoms

A diagnosis in the earliest stages is a matter of the greatest importance for energetic treatment when the disease affects only the membranes and roots and has not spread to the spinal cord may lead to the most satisfactory results If however these subjective symptoms are

ingitis are the most satisfactory cases to treat and usually a hopeful prognosis may be given for the localized process is arrested more readily in its progress by antisyphilitic remedies and the complications which may arise as a result of the cord disease are less severe and less numerous

It is usually the complications which arise that are the immediate cause of death therefore, the prognosis as to prospects of life largely depends upon the present existence or the probable occurrence in the future of the usual complications in severe organic disease of the nervous system e g bronchopneumonia from food inhalation so fatal in all forms of dementia and bulbar conditions bedsores especially the rapidly spreading sacral bedsore occurring in myelitis the bladder troubles with cystitis and pyelonephritis the most fatal of all complications in nervous disease and especially in diseases of the spinal cord But if the prognosis of recovery or death depends so much upon the occurrence of these more or less avoidable complications it must depend in a corresponding degree upon careful treatment and skillful nursing whereby these complications can be prevented or if they cannot be prevented as sometimes happens they should be recognized immediately and not a moment should be lost in endeavors to repair the mischief The prognosis as to the future also largely rests upon the intelligent treatment of paralyzed limbs so that a patient may not from want of skillful treatment remain helpless and bedridden from contracture of his limbs Not only therefore does the prognosis depend upon the symptoms presented by the patient but also upon the patience perseverance and intelligence of the physician and nurse aided by the cooperation of the patient and friends

If the diagnosis be one of parenchymatous neurosyphilis the immediate danger to life is not great but whether the condition be tabes dorsalis or taboparesis, the prognosis is not as good as in most forms of meningovascular neurosyphilis the most that can be hoped for is an arrest of the disease with improvement in symptoms in some cases with later relapse the possibility of complete recovery being too remote for consideration Many cases of tabes dorsalis however remain stationary for some years under the influence of treatment in spite of the tendency for the disease to progress

Alcohol is often an ally of syphilis in the production of disease of the nervous system and unless a patient suffering from neurosyphilis can refrain from alcoholic excess the prognosis is bad Also in forming a prognosis as to the future the liability to emotional stress must be taken into account

Table I

I

Tabes dorsalis

1 Average time between syphilitic infection and onset of symptoms ten years Very rarely under four years Only slight signs if any of syphilitic residua as a rule Onset and course usually slow insidious and progressive

2 Pupillary changes common Argyll Robertson pupil rarely absent

3 Optic atrophy not uncommon

4 Bladder troubles common and visceral crises not infrequent

5 Knee and ankle jerks absent as a rule

6 Lightning pains in body and limbs No stiffness in the neck and spine Girdle sensation may be present and thoracic anesthesia frequently is present in the first stage

7 Positive Wassermann reaction of blood and in cerebrospinal fluid in about 65 per cent of the cases Lymphocytes 60 to 70 per cu mm protein content varies to 0 08 per cent

The blood may yield a negative Wassermann reaction with positive Wassermann reaction in cerebrospinal fluid in 60 per cent of cases while both are negative in about 20 per cent Lange gold sol curve usually luetic is not infrequently paretic

II

Pseudotabes syphilitica

1 Average time between syphilitic infection and onset of symptoms eighteen months to two years rarely after four years Generally signs of syphilitic residua Onset and course usually rapid and subject to regressions and remissions

2 Pupil phenomena and strabismus common but Argyll Robertson pupil rare

3 Optic neuritis and postneuritic atrophy not uncommon A unilateral central scotoma the other eye remaining healthy is an indication of a retrobulbar neuritis affecting the papill macular bundle of fibers it indicates gummatous meningitis

4 Bladder troubles common

5 Knee jerks variable may be absent and return later

6 Spinal pain tenderness and stiffness the pains lancinating radiating from the spine down the limbs Girdle sensation and thoracic anesthesia present very frequently

7 Wassermann reaction usually positive in blood and frequently positive in cerebrospinal fluid Lymphocytes may vary from 10 to 500 per cu mm Protein varies from 0 03 to 0 15 per cent Lange gold sol curve wholly luetic but occasionally paretic

III

Toxic polyneuritis

1 In some cases a history of some toxic condition e g diphtheria typhoid lead diabetes and particularly alcohol

There is pain and tenderness of the limbs and the gait is ataxic there may be paresthesia and often the muscles are wasted There is usually foot drop and possibly wrist drop The pupils are as a rule not affected There are no changes in the fundus in diphtheria there may be paralysis of the muscle of accommodation the light reflex being preserved As a rule there are no bladder troubles The knee jerks may be first present or lost

The blood and cerebrospinal fluid yield negative Wassermann reaction with normal cell count in the latter although protein may be raised

overlooked and their true significance not appreciated the infective inflammation may spread from the membranes along the septa to the spinal cord and cause a myelitis resulting in a group of symptoms which depends upon the situation and extent of the myelitis

Meningomyelitis The symptoms resulting from a meningomyelitis are twofold viz (1) degeneration and subsequently sclerosis of the long afferent and efferent system tracts to and from the brain (2) degeneration and destruction of the spinal cord as a reflex segmental organ The symptoms usually are focal If in the dorsal region there will be a spastic paraplegia with loss of control of sphincters but without any serious symptoms arising from injury of the gray matter If however the lesion is in the lumbosacral region there will be in addition to signs of degeneration of the pyramidal tract system more or less degenerative atrophy of the leg muscles and a more complete loss of control of the sphincters If the myelitis is in the cervical region in addition to root symptoms in the upper limbs and a spastic paraplegia there will be loss of power in the upper limbs with wasting and reaction of degeneration of muscles corresponding to the affection of the segments of gray matter

Tabes Dorsalis The commonest affection of the spinal cord resulting from syphilis is tabes dorsalis A knowledge therefore of the multiform early symptoms of this disease is essential for its diagnosis in the early or preataxic stage A very important matter is the differential diagnosis of tabes and pseudotabes the latter may be due (1) to a gummatous meningitis involving especially the posterior roots or (2) to an ataxic form of peripheral toxic neuritis In both of these diseases there may be considerable ataxia with Romberg s sign The chief points in making a diagnosis may be summarized as is shown in the table on p 541

Myelitis It should be remembered that myelitis due to other causes e g specific fevers microorganisms and microbial toxins may occur in a person who has had syphilis

Poliomyelitis Sometimes a lower motor lesion resembling poliomyelitis may occur as a result of syphilis this could be explained by an obliterative endarteritis of the anterior spinal artery The onset may be sudden owing to thrombosis in the vessel affected by syphilitic disease

Landry s paralysis occurring in the subject of antecedent syphilis might be mistaken for acute ascending myelitis of syphilitic origin but in ascending myelitis sensation is affected and if the patient survives there is a tendency to the formation of bedsores In Landry s paralysis there is little or no impairment of sensation and bedsores do not form

Vertebral Caries It is not uncommon for tubercle and syphilis to

Cases have been described clinically of a primary peripheral peri-endo neuritis gummosa and these have been diagnosed on account of the fact that symptoms of neuritis have occurred in a patient the subject of syphilis palpation has given evidence of nodular thickening in the painful nerves and these signs and symptoms have disappeared under appropriate treatment

Neuralgia Syphilitic neuritis may cause severe neuralgia and neuralgias of the fifth nerve are not infrequent in the early stages of the disease Lang believes that some of these cases of neuralgia of the trigeminal nerve may be occasioned by meningeal irritation The pain may affect one branch or all of the branches of the fifth nerve

In none of these cases of neuralgia from syphilitic neuritis are painful pressure points absent at the point where the nerve emerges from the bone or fascia The branches of the cervical plexus have been known to be affected and especially the great and small occipital and great auricular nerves Neuralgia of the brachial plexus is rare Intercostal neuralgia occurs also neuralgias of the nerves arising from the lumbar and sacral plexuses and the commonest seat of neuralgia after the fifth is the sciatic E Mendel reported three cases of sciatica in syphilitic subjects which were cured promptly by mercury Lang describes a case of sciatica in which he was able to feel the sciatic nerve behind the great trochanter as a greatly thickened nodular band which disappeared together with the pain after local injections of mercury cream He considers that sciatica frequently results from syphilis in all probability a perineuritis is the cause in most cases

Acute Polyneuritis Syphilitica A polyneuritis may occur in early syphilis usually during the secondary stage It would be unjustifiable to diagnose such a condition in a syphilitic subject however unless other well recognized causes were excluded e g alcohol over treatment with arsenic or mercury lead diphtheria etc

SEROLOGICAL AND CYTOLOGICAL METHODS OF DIAGNOSIS

Examination of the cerebrospinal fluid not only assists in the diagnosis of a disease of the nervous system but such an investigation is of para mount importance in the early diagnosis of neurosyphilis as abnormalities in the cerebrospinal fluid may precede by months or years the first appearance of neurological symptoms According to Stokes a figure of from 24 to 26 per cent represents the basic minimum of syphilitics in whom involvement of the nervous system has not disappeared within the first year or two of infection either as a result of treatment or owing

exist in the same individual and cases of syphilitic disease of the vertebræ simulating Pott's disease have been described some of the cases were no doubt tuberculous caries in a syphilitic individual others were possibly syphilitic disease of the vertebra in a tuberculous individual Syphilitic caries of the vertebræ is extremely rare as compared with tuberculous disease

Disseminated Sclerosis This is sometimes one of the most difficult conditions to differentiate from neurosyphilis especially as it occurs in young adults Disorders of gait and spastic paresis of the limbs may be present There is in addition absence of abdominal reflexes extensor plantar reflexes together with a history of paresthesia preceding the motor symptoms Even without the physical signs of nystagmus intention tremors and pallor of the optic discs a diagnosis of the spinal form of this disease is permissible but in order to determine the differential diagnosis examination of the cerebrospinal fluid is essential Absence of excess of lymphocytes and a negative Wassermann reaction exclude syphilis although the Lange gold sol curve may be positive

Hysterical paraplegia may be differentiated in the same way if there be any doubts but usually the diagnosis is easy owing to the fact that the deep and superficial reflexes are normal the sensory troubles do not correspond to segmental root or nerve distribution the sphincters are not affected and the symptoms being due to suggestion can be removed by counter suggestion

Symptomatology of Syphilis of the Peripheral Nerves

A secondary affection of the peripheral nerves may occur owing to syphilitic disease of the bones lymphatic glands fasciæ and muscles The nerves may be irritated causing pain and hyperesthesia or paresthesia or motor spasm according as the function of the nerve is sensory or motor or sensori motor a nerve may be so damaged by compression or the extension of inflammation as to lose its conductile functions and anesthesia and paralysis result A nerve compression from periostitis syphilitica is diagnosed more often clinically than anatomical facts warrant

It is conceivable that syphilitic periostitis may so affect the intervertebral foramina as to cause symptoms pointing to affections of the nervous structures passing through

Not only may compression by syphilitic inflammatory deposits cause a local pressure atrophy but even more important in the production of symptoms is the extension of the inflammation to the epi peri and endoneural lymphatics causing thereby a spreading neuritis

the globulin which is in such small quantity as to give no reaction with the usual tests (Nonne Pandy and Noguchi) Under normal conditions the total protein content of the cerebrospinal fluid obtained by lumbar puncture varies from 0 0 to 0 035 per cent the higher figure tending to occur in the more elderly patients Carnegie Dickson finds that the total protein content is lower in cerebro spinal fluid obtained by cisternal and by ventricular puncture and gives 0 01 to 0 025 per cent as the normal range for cisternal fluids and 0 005 to 0 0 per cent for ventricular fluids the higher figures again occurring in older patients

When an inflammatory or infective condition affects the central nervous system the permeability of the barrier between the blood and cerebrospinal fluid is increased allowing larger globulin molecules to pass through with relative increase in the globulin content

In meningovascular neurosyphilis the total protein may show an increase from 0 05 to 0 15 per cent with moderately positive globulin reactions In tabes dorsalis the amount of protein usually is moderate (0 03 to 0 05 per cent) while in taboparesis and general paresis the quantity varies from 0 05 to 0 1 per cent with strongly positive globulin tests

Lange in 1912 elaborated the colloidal gold reaction or gold sol reaction in the cerebrospinal fluid as a result of the application of Zsigmondy s observations on the protective action of colloids on the precipitation of gold suspensions by sodium chloride Other colloidal preparations benzoin and mastic have been used also but colloidal gold remains the most sensitive and reliable substance and Lange s test the method of choice In this reaction the two characteristic curves of neurosyphilis are the luetic in which the more pronounced changes occur in the third to fifth tubes of the series (1233210000 or 1244321000) and the paretic in which the earlier tubes show maximal changes the solution being completely or almost completely decolourised (4433210000 and 5555432100)

A pronounced paretic curve is very characteristic of general paresis and usually occurs in association with strongly positive Wassermann reaction increased protein (0 05 to 0 1 per cent) globulin reaction to excess and increase in cell content up to 60 per cu mm This type of curve also occurs in taboparesis occasionally in tabes dorsalis and not infrequently in diffuse syphilitic meningitis as well as in acute neuro recurrences of meningovascular type The luetic curve is found in most cases of tabes dorsalis in the various forms of meningovascular neurosyphilis and in latent or asymptomatic neurosyphilis

As with the Wassermann reaction all cerebrospinal fluid changes cells total protein globulin and Lange curve may be modified considerably towards the normal as the result of antisyphilitic treatment

to the natural resistance of the patient It is the members of this group that will show later the manifestations of neurosyphilis either meningo vascular or parenchymatous Consequently often there is no definite relation between the severity of symptoms and the intensity of the cerebrospinal fluid changes A case with gross abnormalities in the cerebrospinal fluid may present only mild symptoms or even be completely asymptomatic while one with severe symptoms may yield a normal cerebrospinal fluid

The Wassermann reaction in the cerebrospinal fluid varies considerably In early meningovascular neurosyphilis often it is negative in other cases the Wassermann reaction may be strongly positive to become negative later as a result of treatment The cerebrospinal fluid Wassermann reaction is more likely to be positive in the parenchymatous forms of neurosyphilis in general paresis Mott (1916) obtained positive results in 98 per cent and Brown and Mackenzie (1924) in 91 per cent of cases

In all forms of neurosyphilis some cases occur in which the blood yields a positive Wassermann reaction while the cerebrospinal fluid is negative the reverse positive Wassermann reaction in cerebrospinal fluid and negative blood is less frequent and more likely to be met with in neurosyphilis of the parenchymatous type Even in general paresis cases may occur in which the blood is negative while the cerebrospinal fluid yields a positive result

The presence or otherwise of a positive Wassermann reaction in the cerebrospinal fluid or its intensity has no definite relation to the differential diagnosis between meningovascular and parenchymatous neurosyphilis The outstanding difference between these two forms of neurosyphilis undoubtedly is the fact that meningovascular lesions yield more readily to antisyphilitic treatment

The cell count is an index of the meningeal (leptomeninges) reaction The typical cell is the small lymphocyte but occasionally large lymphocytes may be found as well as plasma cells and endothelial cells from the arachnoid A cell count from 6 to 10 per cu mm is suspicious while excess is represented by more than 10 cells the figure may reach 1 500 or more In acute diffuse syphilitic meningitis the abnormal number of cells may give rise to a turbid cerebrospinal fluid in which even polymorphonuclear cells may be found while in basal meningitis cells up to 1 000 per cu mm is not uncommon

The total amount of coagulable protein in the cerebrospinal fluid is estimated conveniently by Mestrezat s opacity method In normal cerebrospinal fluid the amount of albumin is considerably in excess of

the globulin which is in such small quantity as to give no reaction with the usual tests (Nonne Pandy and Noguchi) Under normal conditions the total protein content of the cerebro spinal fluid obtained by lumbar puncture varies from 0.02 to 0.035 per cent the higher figure tending to occur in the more elderly patients Carnegie Dickson finds that the total protein content is lower in cerebro spinal fluids obtained by cisternal and by ventricular puncture and gives 0.01 to 0.025 per cent as the normal range for cisternal fluids and 0.005 to 0.02 per cent for ventricular fluids the higher figures again occurring in older patients

When an inflammatory or infective condition affects the central nervous system the permeability of the barrier between the blood and cerebrospinal fluid is increased allowing larger globulin molecules to pass through with relative increase in the globulin content

In meningovascular neurosyphilis the total protein may show an increase from 0.05 to 0.15 per cent with moderately positive globulin reactions In tabes dorsalis the amount of protein usually is moderate (0.03 to 0.05 per cent) while in taboparesis and general paresis the quantity varies from 0.05 to 0.1 per cent with strongly positive globulin tests

Lange in 1912 elaborated the colloidal gold reaction or gold sol reaction in the cerebrospinal fluid as a result of the application of Zsigmondy's observations on the protective action of colloids on the precipitation of gold suspensions by sodium chloride Other colloidal preparations benzoin and mastic have been used also but colloidal gold remains the most sensitive and reliable substance and Lange's test the method of choice In this reaction the two characteristic curves of neurosyphilis are the luetic in which the more pronounced changes occur in the third to fifth tubes of the series (1233210000 or 1244321000) and the paretic in which the earlier tubes show maximal changes the solution being completely or almost completely decolourised (4433210000 and 5555432100)

A pronounced paretic curve is very characteristic of general paresis and usually occurs in association with strongly positive Wassermann reaction increased protein (0.05 to 0.1 per cent) globulin reaction to excess and increase in cell content up to 60 per cu mm This type of curve also occurs in taboparesis occasionally in tabes dorsalis and not infrequently in diffuse syphilitic meningitis as well as in acute neuro recurrences of meningovascular type The luetic curve is found in most cases of tabes dorsalis in the various forms of meningovascular neurosyphilis and in latent or asymptomatic neurosyphilis

As with the Wassermann reaction all cerebrospinal fluid changes cells total protein globulin and Lange curve may be modified considerably towards the normal as the result of antisyphilitic treatment

TREATMENT

General Methods of Treatment

The general treatment of syphilitic diseases of the nervous system is based upon the same principles that serve as the guide to treatment in non syphilitic diseases The diet should be nutritious and as a rule alcoholic drinks should be avoided or taken only in small quantities When the patient is suffering from bulbar symptoms great care must be exercised in feeding soft moist food should be given and meat or food requiring mastication should be minced or made into a paste otherwise alarming symptoms may arise from choking fluids are better given with a teaspoon than by a feeding cup There is always danger of fluids passing into the air passages and owing to the insensitive condition of the mucous membrane or the paralytic condition the protective expulsion by coughing either does not occur or is ineffectual Especially should great care be exercised by the nurse in feeding patients in a semiconscious somnolent condition inhalation bronchopneumonia is a frequent cause of a fatal termination from neglect of these precautions In the semi conscious condition or coma it is better to administer no nutrient fluids by the mouth if they are necessary they can be given in the form of enemata

In severe cases the patient should be put to bed the room should be darkened and noise and excitement of all kinds avoided these precau tions are particularly necessary in cerebral cases

The successful treatment of the case not only depends upon the early diagnosis and antisyphilitic treatment but also upon good nursing by which complications may be avoided the most important of these besides bronchopneumonia are bedsores and cystitis The nurse in charge should be cautioned particularly against the dangerous results which may arise from neglect of the following precautions The patient if helpless and bedridden should be placed on a water bed as soon as possible sometimes this is not possible or the patient feels it so uncom fortable as to object to its use and then greater care must be exercised in avoiding continuous pressure upon one spot Bedsores are especially liable to form over the sacrum and spread rapidly in cases of spinal paraplegia and sometimes in spite of all precautions a bedsore occurs

The back the heels and buttocks should be examined daily and a red spot appearing should always be a danger signal to the nurse The phy sician should take measures immediately to prevent further developments The skin especially of parts subjected to pressure should be washed

daily with soap and water and moistened with spirit or eau de Cologne finally carefully dried and powdered with kaolin or zinc oxide One of the most fruitful causes of bedsores is carelessness in allowing the patient to lie on sheets soiled with urine and feces Since incontinence of the bladder and bowels is so frequent in paralytic conditions measures must be adopted to prevent the patient lying in decomposed urine and in feces Urinals fixed on the penis are objectionable sometimes owing to the organ being continually exposed to the action of decomposing urine sloughing of the foreskin and other complications may arise It is much better to arrange absorbent antiseptic wool or oakum under the perineum in such a way that it may collect and absorb the urine and fece which escape in consequence of paralysis of the sphincters or incontinence

In spite of all precautions by doctors and nurses bedsores will arise occasionally and they call for energetic measures or the septic process may rapidly spread to the bone and membranes causing an infective spinal meningitis When a red spot appears zinc ointment may be applied on lint fixed with plaster and the patient should be so arranged in his bed that pressure is taken off the inflamed spot Should a slough be formed and a septic process of ulceration invade the subcutaneous tissues boracic acid fomentations or charcoal poultices may be used they should be changed continually and every endeavor made to get a healthy granulation tissue

Even more common and quite as dangerous as the occurrence of bed sores is cystitis from retention and decomposition of the urine in the bladder this may be the result of catheterization but it often occurs in cases e g tabes dorsalis and meningomyelitis where the catheter has never been used The occurrence of intermittent pyrexia always should suggest to the mind of the practitioner the probability of a septic condi tion of the bladder which may if neglected go on to a fatal pyelonephri tis In every case the condition of the bladder should be determined the dribbling away of water continuously in a semiconscious patient may really be due to retention of urine with overflow and the patient not being in a fit state of mind to complain may be suffering from a greatly distended bladder I have seen such cases in which the bladder has reached to the umbilicus the use of the catheter therefore may be required and if it is great care should be exercised in seeing that it is quite sterile Should cystitis have occurred owing to the residual urine having undergone decomposition and the water passed be ammoniacal and alkaline immediate measures should be taken to combat this con dition before it sets up a secondary pyelonephritis The bladder should be washed out daily with a weak boric acid solution followed by in

jection of 4 or 5 oz (120 to 150 c c) of peroxid of hydrogen 10 vols urotropin 10 grs (0 6 gm) combined with half to one dram (2 to 4 gms) of borocitrate of magnesia or acid phosphate of soda should be administered three times a day By this treatment the cystitis usually can be cured The bowels should be attended to in some cases there is obstinate constipation and purgatives are required

When there is hemiplegic or paraplegic contracture a great deal of improvement in power can be obtained by massage and passive movements the patient should be instructed to attempt active movement which is being passively performed by the operator he is to try to assist in the movement in this way the path to the limb from the brain may be reopened or a new path established A great deal of the immobility of limbs comes from disuse of the limbs and neglect to free the joints Another practical hint most useful in restoring movement in the lower limbs in paraplegia is always to take off the weight of the bed clothes by a cradle and wrap the limbs in wool or woollen knitted stockings and prevent foot drop by a support against the soles of the feet in this way contracture of the calf muscles is prevented Massage and movements may be undertaken when the acute symptoms have passed off and as soon as possible the patient should be encouraged to put the feet on the ground and learn to walk holding on to the back of a wheel chair

Insomnia and *restless motor activity* may necessitate the use of hypnotics and narcotics Among the drugs used to produce sleep may be mentioned sulphonal veronal (barbital) medinal (barbital sodium) trional bromide chloral and paraldehyde When the insomnia is due to pain these remedies usually are inefficient and it may be necessary to give morphia hypodermically by mouth or by suppository the last named mode of administration is useful for pains in the pelvis and back It is essential to keep the patient warm and he should wear warm underclothing and if he is well off he should be recommended to pass the winter in a warm dry equable climate When convalescent it is advisable to point out to the patient that however well he may feel he has an invalid nervous system and should avoid all causes of stress mental or physical he must lead a regular simple life and particularly should he avoid alcoholic and sexual excess

In cases where epileptic fits have supervened on old syphilitic disease of the brain bromides or phenobarbital (luminal) may be administered Very often this remedy fails to control the fits and if there be definite localizing evidence of a focal gumma or scar in the neighborhood of the motor area the question of surgical treatment should be considered

especially if mercury and iodides have failed to produce further amelioration Antisyphilitic drugs have no influence in causing absorption of dense fibrous tissue in the brain resulting from a healed gumma the scar tissue will continue to act as an irritant in spite of specific treatment Operation might be considered under the following circumstances (1) Persistent symptoms and signs of cerebral tumour in spite of a prolonged course of antisyphilitic treatment (2) Even when other general signs of cerebral tumour have disappeared viz headache vomiting and papilloedema under the influence of antisyphilitic treatment the persistence of Jacksonian epilepsy This may result from a pachymeningitis or a healed gumma in the neighbourhood of the motor area or in the motor region itself in the latter case there probably would be an associated monoplegia or monoparesis

Drug Treatment

General Principles of Treatment The diagnosis of the nature of the syphilitic lesion having been made it is necessary to decide upon the mode of specific treatment It is better to have no rigid scheme but be guided by general principles dependent upon the age health sex and weight of the patient together with the character and intensity of the neurosyphilitic affection and the history of previous treatment for syphilis or otherwise The importance of an examination of the cerebrospinal fluid has been emphasized already in the diagnosis of affections of the nervous system as well as in affording indications of progress and success of treatment

As regards the arsenical preparations it is essential that a thorough and general clinical examination be made prior to their application Disease of the lungs of the heart or the arteries and especially of the kidneys calls for special attention and care It must be borne in mind that in a certain proportion of cases of neurosyphilis involvement of these organs occurs In the presence of advanced arteriosclerosis or severe cardiac or renal disease the arsphenamines are contraindicated A trace of albumin with no casts or only a few hyaline casts may exist in syphilitic patients or the albuminuria may be of the functional type Considering that in fatal cases following arsphenamine injection the kidneys are found to contain more arsenic than all the other organs of the body it follows that even a trace of albumin should make one cautious in the administration of arsphenamine mercury or bismuth The urine should be tested during treatment and any indication of albumin or a tendency to increase the trace of albumin present prior to treatment and the appearance of

jection of 4 or 5 oz (120 to 150 c c) of peroxid of hydrogen 10 vols urotropin 10 grs (0 6 gm) combined with half to one dram (2 to 4 gms) of borocitrate of magnesia or acid phosphate of soda should be administered three times a day By this treatment the cystitis usually can be cured The bowels should be attended to in some cases there is obstinate constipation and purgatives are required

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obtained This 'driblet' method has been advocated also by Harrison Sicard claimed that in chronic neurosyphilis the results were superior to those obtained by weekly intravenous injections and the Wassermann reaction in the blood and cerebrospinal fluid showed a better result by repeated small doses every two days for a period of two months than by weekly injection He does not believe that small doses produce an arseno resistance as experiments seem to indicate

The Possible Toxic Incidence of Intensive Treatment Whether Given Intravenously Weekly or by Repeated Small Doses Every Other Day A slow progressive intoxication by the arsenic may be manifested by the following signs (1) Erythematous rashes are symptoms of the terminal phase of the treatment and indicate an interruption of further injections for at least eight to ten weeks they also point to caution being exercised in further administration (2) An early indication of the toxic action of the arsenic on the peripheral nerves is the disappearance of the tendo Achillis jerk although there is no paresis or necessarily any subjective sensory disturbances (3) Jaundice which usually clears up in from three to four weeks In pushing treatment these signs of toxic effects should be looked for carefully

Considering the immense number of cases which have been treated successfully by intensive methods we should not be deterred from using this valuable mode of treatment of neurosyphilis by the fact of occasional accidents

Intrathecal Treatment

Intrathecal Injection of Serum Salvarsanized in Vivo — In 1911 independently Swift and Ellis Marinesco Fisher and George Robertson introduced the method of intrathecal injection of serum salvarsanized in vivo

The following is the technique described by Swift and Ellis One hour after the termination of an intravenous injection of neosalvarsan or after arsphenamine compound 40 c c of blood are withdrawn direct into flask formed centrifuge vessels after allowing the blood to clot it is centrifuged The next day 12 c c of the serum are pipetted off and diluted with 18 c c of normal saline This 40 per cent serum is then warmed to 56 C for half an hour to inactivate it Lumbar puncture is performed and cerebrospinal fluid is withdrawn until the pressure falls to 30 mm A calibrated syringe capable of holding 30 c c is connected by an india rubber tube 40 cm long with the needle which has been introduced into the subarachnoid space In order to avoid the possibility of the entry of air fluid is allowed to fill the tube Serum is poured into

inces which especially affect the face These last from a few seconds to several minutes Sometimes the attack is accompanied by general tremors nausea vomiting and pyrexia this reaction constitutes the nitroid crisis of Milian Another sign of predisposition to arsenic intolerance is the appearance of an erythematous rash after the first dose

(2) Therapeutic shock or the Herxheimer Jarisch reaction' The luetin reaction of Noguchi showed that the endotoxins of dead spirochetes could produce a local inflammatory reaction also it is presumed that arsenobenzol compounds bismuth and mercury act beneficially by causing a dissolution of the spirochetes this gives rise first to a local inflammatory reaction in the neighbourhood of the seat of the organisms and secondly to a generalized effect on all the tissues of the body by the escape of the endotoxins or their solution into the blood and lymph streams and in the case of the central nervous system by escape into the cerebrospinal fluid It is known that the first effect of mercury is sometimes to intensify the secondary rash and to produce tonsillitis even headache and slight or grave meningeal symptoms sometimes may be intensified but not nearly to the same degree as after the intravenous administration of neoarsphenamine which owing to its greater spirillocidal action causes a much larger amount of endotoxic substance to be liberated

The earliest emphasis of this reaction had been on the cutaneous manifestation of syphilis but later it was realised that such therapeutic shock can occur in any other structure involved by the disease at all stages In the treatment of neurosyphilis especially early diffuse meningitis the liability to a Herxheimer Jarisch reaction must be borne in mind Dreyfus Leredde Werther and others pointed out the desirability of beginning treatment with small doses of arsphenamine preparations and increasing the dose gradually in order to avoid such reactions Some observers e g Werther advise the use of bismuth or mercury for two or three weeks before starting neoarsphenamine injections

(3) Anaphylaxis The reactions of an anaphylactic character often are serious and may be fatal They are characterized by convulsive movements pulmonary œdema and coma Anaphylactic shock occasionally occurs on the next day or the day after the second or third weekly injection

Sicard found that in 200 to 300 cases of neurosyphilis treated exclusively by small repeated doses of neosalvarsan he did not meet with a single case of anaphylactic shock The preparations used were novarsenobenzol galyl and sulfarsenol and the dose employed was 0 15 to 0 2 gm In this way a total dosage of 8 gm of the medicament can be

only slightly spirillocidal It is used chiefly in the parenchymatous forms of neurosyphilis Moore Robertson and others having shown that the drug is ineffective in the various forms of systemic syphilis It has been thought to act more by its resistence producing power than by any direct chemotherapeutic action the work of Voegtlin and others indicates that some part of its efficacy may lie in its ability to penetrate into the central nervous system through the meninges Tryparsamid is given intravenously in doses of from 1 0 to 5 0 gm dissolved in 5 to 10 c c of distilled water the optimum adult dose being 3 gm The substance is most used following a course of malaria in general paresis

Pyrexial therapy either by means of induced malaria electropyrexia or by intramuscular injections of sulfosan and intravenous injections of non specific vaccines is more applicable to those parenchymatous forms of neurosyphilis represented by general paresis and taboparesis

NEURORECURRENCE

A sudden relapse of an inadequately treated neurosyphilis is termed a neurorecurrence The relapse may assume any form of neurosyphilis but involvement of the cranial nerves especially an ocular palsy or facial paralysis is very frequent The remedy lies in a more intensive method of treatment

It should be noted that even after prolonged and intensive treatment the blood may still yield a positive Wassermann reaction but if the cerebrospinal fluid shows a positive reaction as well as the blood the outlook is more seriou even though the patient may exhibit no symptoms or signs A persistently positive Wassermann reaction in the blood does not appear to be of as great importance as that in the cerebrospinal fluid on the other hand the continued presence of a negative blood Wassermann reaction and the propagation of healthy children are not evidences of cure as many cases of tabes dorsalis and even a few cases of ultimate general paresis could pass such a test The difficulty in some cases is to determine when treatment may safely be terminated Some authorities e g F Buzzard consider that since no reliable data on which cure or eradication can be based patients should continue intermittent treatment for the rest of their lives Each case must be judged individually however as there is good evidence that the more thorough and prolonged the initial treatment up to the persistence of negative Wassermann reactions in blood and cerebrospinal fluid the less likely and the more delayed are the more serious forms of neurosyphilis

the syringe and connection is made with the tube the serum is allowed slowly to enter the subarachnoid space by the pressure of gravity By this method any sudden increase of intraspinal pressure is avoided According to Swift and Ellis the most marked result is the great diminution in the number of cells present the positive Wassermann reaction in 41 per cent of their cases disappeared and in nearly all the others was diminished the globulin reaction was the most persistent The stronger the Wassermann reaction was at the beginning of treatment the more difficult was it to render the fluid negative

Fordyce modified the method of Swift and Ellis and claimed a satisfactory result for this method of treatment He added salvarsanized serum to 30 or 40 c c of withdrawn cerebrospinal fluid and allowed the mixture to return by gravity

It is probably the traces of arsenobenzol in the salvarsanised serum' that give rise to any favourable results for neosalvarsan in very small doses has been injected into the subarachnoid space with alleged beneficial effect by Ravaut Wechselmann and Marinesco originally used this latter method in 1912 but gave it up on account of serious complications

The Swift Ellis method of intrathecal treatment is not widely used but is applicable to some cases of tabes dorsalis (see Chapter XX)

Intrathecal Injection of Hypertonic Solution of Neosalvarsan Ravaut reintroduced this method of treatment first employed by Wechselmann but modified it by employing a hypertonic solution of 3 mgm of neosalvarsan in 1 drop of water He injected from 1 to 4 drops of this hypertonic solution which was made freshly at the moment of injection For this purpose he dissolved 0 3 gm in 5 c c of water The largest dose tolerated was 6 mgm and a series of six intrathecal injections each of 3 to 6 mgm one being given every eight days was the usual course Ravaut claimed that in all cases there was a parallelism between the subsidence of clinical signs and symptoms and the improvement in the reactions of the cerebrospinal fluid

The intrathecal administration of even such weak solutions of neoarsphenamine however is not to be recommended The results may be too serious and the writer has seen permanent flaccid paraplegia probably due to destruction of the cauda equina ensue shortly after such an injection

Other Methods of Treatment

Tryparsamid synthetised by Jacob and Heidelberger in 1917 and a relative of atoxyl is one of the most powerful trypanocides known but is

CHAPTER XX

TABES DORSALIS

By SIR FREDERICK W. MOTT

Revised and Partly Re-written by C. Worster Drought

Table of Contents

Synonyms — Locomotor ataxia posterior spinal sclerosis

Definition — A progressive degeneration of the nervous system involving the posterior roots and their intraspinal projections within the posterior columns causing various sensory disturbances including muscular incoordination and disorder of gait and station

History

Hippocrates and his followers spoke of φθίσις νωτιάς indicating a wasting disease of the spinal cord they attributed it to the loss of sperm the result of onanism or venereal excesses This affection probably was a neurosis as it is doubtful if true tabes ever existed in Europe before the introduction of syphilis in the fifteenth century

The original article Chapter XIX extended to page 558 but this revision ends with page 555

locomotor ataxy was everywhere a recognized disease in medicine Still every year since has brought forth fresh observations showing the protean nature of this disorder and although in many books it is still called by the name given it by Duchenne nevertheless locomotor ataxy although it expresses a very characteristic feature of the disease has this objection it is a symptom which does not occur in the first stage (preataxic) of the disease indeed a long period of time may elapse before ataxia appears and sometimes the patient after suffering a great number of years from the disease may die from some intercurrent complication having never been ataxic Hughlings Jackson in 1881 when discussing the eye symptoms in tabes stated There are many cases of locomotor ataxy without ataxy for these cases locomotor ataxy is strictly a misnomer tabes dorsalis is better since it covers cases with and without abnormal gait

It is impossible even to enumerate the history of all the important additions which have been made to our knowledge of this disease but there still remain some few which require mention

Of especial importance were the discoveries of the reflex pupil rigidity by Argyll Robertson (1869) and the absence of the knee jerk by Westphal in 1875 Gastric crises had been described by Delamare in 1866 but it was Charcot (1868) who gave a masterly description of this symptom as well as of the arthropathies this was extended later to spontaneous fractures (1873) and the tabetic foot (1883) Duplay and Morat pointed out the perforating ulcer in 1873 As the clinical knowledge of the condition has extended so also has the macroscopic and microscopic anatomy Knowledge of the minute anatomy of the morbid changes in tabes may be said to have been begun by Virchow in 1855 and Rokitansky in 1857 The latter described it as a proliferation of the structureless ependyma like connective tissue and stroma of the nerve centers which caused destruction of the nerve elements proper and resulted in induration or sclerosis of the affected parts But Bourdon and Luys were the first to make important microscopical investigations in reference to the well defined group of symptoms in tabes They described the condition as sclerosis of the posterior roots the final result of a chronic inflammatory process Von Leyden (1863) however maintained that it had more the characters of a simple atrophy and the inflammatory changes which might be seen in the membranes and around the vessels were either secondary or accidental

Pierret 1871 observed that the primary lesion of tabes did not consist in a degeneration of the posterior columns as a whole but in two symmetrical islets of small extent situated in a special region of the posterior column les bandelettes externes of the columns of Burdach thus tabes came for a time to be considered as a system disease or sclerosis of

In Germany and France true descriptions of the disease were given almost simultaneously and certainly independently by various observers To Cruveilhier (1835 1842) belongs the merit of having described in his studies upon paraplegia the case of a woman aged 52 with anesthesia of the legs with stumbling gait painless fracture of bones etc at the post mortem examination a yellowish gray degeneration of the spinal cord was found which involved the whole of the posterior columns in the lower part but only the median portion in the cervical region The important point is that Cruveilhier connected the sensory disturbances observed during life with this degeneration of the posterior columns Gowers gives to Todd the credit of the discovery of this disease Certainly Todd 1847 drew a clear distinction between paralysis and incoordination and was the first to connect incoordination with disease of the posterior columns of the spinal cord yet one must agree with Mobius and Ferrier in assigning the first place to Romberg (1840–1857) for there is no doubt that he first gave a systematic account of the etiology symptomatology diagnosis prognosis and treatment of tabes In his Lehrbuch der Nervenkrankheiten he describes the characteristic gait the pathognomonic symptom now called by his name the increase of the ataxia on closing the eyes the shooting pains anesthesia and paresthesia the bladder troubles the affections of vision and the striking myosis and fixity of the pupils He mentions the relative infrequency of tabes in women and as to prognosis he utters the gloomy verdict to none affected by this malady is there any hope of recovery uber alles ist der Stab gebrochen He noted the atrophy of the spinal cord especially of the lower part of the lumbar enlargement He also described atrophy of the cauda equina and what is of still greater interest he observed that the posterior roots sometimes are affected alone at other times along with the posterior columns while the anterior roots appear normal Romberg however did not clearly differentiate the basis of ataxia from that of muscular paresis or paralysis

Duchenne 1858 by his masterly clinical genius clearly differentiated the affection from muscular paralysis or paresis occurring in the various forms of so called general spinal paralysis and unclassified forms of chronic myelitis naming it after the most striking symptom ataxie locomotrice progressive Trousseau in his lectures spread abroad the knowledge of the affection which Duchenne had vivified in his published researches on ataxie locomotrice calling it Duchenne s disease thereby doing scant justice to previous observers

As to priority it may be said that the knowledge of tabes grew independently in all three countries and from the year 1860 onwards tabes or

Microscopic Appearances — The spinal cord lesions of tabes and taboparesis as regards the affection of the posterior roots and posterior columns are as a rule identical In both diseases there is the same system of exogenous fibers affected in the same situations in the spinal cord The morbid process selects first certain groups of fibers and spares others but eventually in advanced cases destroys nearly all the exogenous fibers Many symptoms and signs and especially the distribution of anesthesia in the cases of tabes and taboparesis in which the cutaneous sensibility can be ascertained indicate that certain segmental regions of the spinal cord are affected earliest and systematic microscopic examination of the spinal roots and of the spinal segments shows that certain regions are more affected than others viz lower lumbar and sacral upper middorsal and lowest cervical

Microscopic examination almost invariably shows whether the case is early or late that degeneration or disappearance of fibers has taken place in the lumbrosacral region of the cord relatively proportional to the atrophy of the exogenous system The bundles of posterior roots which normally are considerably larger than the anterior roots are much smaller and diminished in size in proportion to the outfall of fibers The interstitial tissue sometimes is increased although there is not always a proliferation the vessels often are seen engorged with blood but not more so than those of the undegenerated anterior roots The wall of the arteries and arterioles often are normal when thickened owing to arteriosclerosis it is generally in a subject over fifty and the thickening is not limited to the posterior roots but affects also the arteries of the comparatively healthy anterior roots

The appearance of the posterior root fibers presents the condition found in a nerve after section when all the products of degeneration have been absorbed Empty neurilemmal sheaths with proliferated nuclei vessels and connective tissue are the only structures found as a rule in the roots which have undergone degenerative atrophy Some fibers still possessing a myelin sheath may be found amidst this tissue if the root fibers are not destroyed completely The degenerative atrophy extends back as far as the spinal ganglion yet the atrophic process commences at the terminal arborizations in the spinal cord

The attractive theory of Marie based upon the neuron doctrine that the degeneration is due to a nutritional change in the posterior spinal ganglion cells is one which explains many facts but the argument which is advanced against it is that numerous observers have asserted that the changes which have been found were insufficient to account for the changes in the roots and cord

the posteroexternal columns Vulpian, 1879 however maintained that a primary degeneration of the posterior columns could not lead to atrophy of the posterior roots seeing that their trophic center was in the posterior spinal ganglia and he therefore regarded the atrophy of the roots as of primary origin

Morbid Anatomy of the Spinal Cord and Peripheral Nerves in Tabes Dorsalis and Taboparesis

Macroscopic Appearances — Upon opening the spinal canal in an advanced case of tabes the most obvious changes noticeable are the flattening of the cord and the gray wasted appearance of the posterior roots of the cauda equina and of the dorsal and lower cervical regions the soft membranes also are thickened in the dorsal aspect When the cord is removed with the posterior spinal ganglia there is a marked contrast observable in the appearance of the anterior and posterior roots and the anterior and posterior aspects of the spinal cord whereas the anterior roots are white and are of normal thickness the posterior (normally twice the size of the anterior) are gray and greatly diminished in thickness The anterior aspect of the cord is normal or nearly normal in appearance the posterior is shrunken and often owing to the shrinkage concave in the middle the membranes are thickened and the posterior columns have a gray appearance The cord when cut transversely exhibits a gray degeneration of the posterior columns and a shrinking and hardening of them so that the two posterior horns of gray matter which also are atrophied are closer together than normal Although the posterior roots are much atrophied the spinal ganglia do not present any obvious naked eye change nor can obvious naked eye change be seen as a rule in the peripheral nerves The gray degeneration of the posterior columns can be followed as far as the nuclei of Goll and Burdach and the atrophy of the terminal fibers around the cells of these nuclei produces a change in the shape of the medulla in these regions owing to the sclerosis resulting in consequence of the atrophy In some cases of taboparesis the atrophy is limited to the posterior columns in others and more rapid cases the whole cord is wasted and there is comparatively little glia proliferation In some cases of tabes dorsalis which have terminated in general paresis and especially when epileptiform seizures have occurred there is not only a naked eye sclerosis of the posterior columns but also a shrinking and sclerosis of one or both lateral columns if the seizures have been unilateral the fiber degeneration and atrophy is on the same side as the seizures

Microscopic Appearances — The spinal cord lesions of tabes and taboparesis as regards the affection of the posterior roots and posterior columns are as a rule identical In both diseases there is the same system of exogenous fibers affected in the same situations in the spinal cord The morbid process selects first certain groups of fibers and spares others but eventually in advanced cases destroys nearly all the exogenous fibers Many symptoms and signs and especially the distribution of anesthesia in the cases of tabes and taboparesis in which the cutaneous sensibility can be ascertained indicate that certain segmental regions of the spinal cord are affected earliest and systematic microscopic examination of the spinal roots and of the spinal segments shows that certain regions are more affected than others viz lower lumbar and sacral upper middorsal and lowest cervical

Microscopic examination almost invariably shows whether the case is early or late that degeneration or disappearance of fibers has taken place in the lumbrosacral region of the cord relatively proportional to the atrophy of the exogenous system The bundles of posterior roots which normally are considerably larger than the anterior roots are much smaller and diminished in size in proportion to the outfall of fibers The interstitial tissue sometimes is increased although there is not always a proliferation the vessels often are seen engorged with blood but not more so than those of the undegenerated anterior roots The walls of the arteries and arterioles often are normal when thickened owing to arteriosclerosis it is generally in a subject over fifty and the thickening is not limited to the posterior roots but affects also the arteries of the comparatively healthy anterior roots

The appearance of the posterior root fibers presents the condition found in a nerve after section when all the products of degeneration have been absorbed Empty neurilemmal sheaths with proliferated nuclei vessels and connective tissue are the only structures found as a rule in the roots which have undergone degenerative atrophy Some fibers still possessing a myelin sheath may be found amidst this tissue if the root fibers are not destroyed completely The degenerative atrophy extends back as far as the spinal ganglion yet the atrophic process commences at the terminal arborizations in the spinal cord

The attractive theory of Marie based upon the neuron doctrine that the degeneration is due to a nutritional change in the posterior spinal ganglion cells is one which explains many facts but the argument which is advanced against it is that numerous observers have asserted that the changes which have been found were insufficient to account for the changes in the roots and cord

It may be stated generally that the peripheral cerebrospinal nerves like the spinal cord of advanced cases of taboparesis are smaller in transverse section than normal and without any microscopic examination it would be said that they are atrophied Transverse and longitudinal sections in some advanced cases may show changes but in no degree sufficient to account for the symptoms or in any way proportional to the atrophy of the posterior roots

In twenty eight spinal cords of cases of tabes and taboparesis examined by Mott the three sets of coarse fibers entering the cornuradicular zone and proceeding respectively to the root zone of Charcot to the cells of Clarke s column and to form Goll s column were affected not always however to the same extent for the relative degree of degeneration of each of these three systems of fibers depends upon the relative degree of degeneration of particular roots For although every root in the lumbosacral region where the morbid process in the great majority of cases commences contains fibers belonging to each of the three systems namely spinal cerebellar and cerebral yet some roots according to the functions of the structures innervated by them contain many more cerebral afferent fibers than cerebellar and vice versa

The ataxia may have a decided relationship to the atrophy of the plexus around the cells of Clarke s column for Mott saw no case in which this was pronounced without marked ataxia whereas he saw other examples in which this symptom was not pronounced although Goll s column was affected markedly

The fine fibers of Lissauer s tract are not affected in all cases of tabes in eleven cases out of twenty eight spinal cords examined by Mott the fine fibers of Lissauer s tract were affected but slightly whereas in all cases there was a marked affection of the cornuradicular zone A correlation of sensory skin disturbance observed during life and atrophy of Lissauer s tract of fibers was however observed by Mott in a number of cases The path of sensibility of deep structures from muscles tendons and ligaments and structures about joints is especially affected in tabes and occasionally as Redlich and others have observed in early cases terminating fatally acute changes may be found affecting the intramedullary portion of the exogenous neurons and not the roots An example of this occurred in Mott s practice A taboparetic patient did not long survive the onset of spinal symptoms and Mott found upon microscopic examination of the spinal cord a number of recent degenerated intramedullary fibers in the lumbosacral region limited to (1) the cornuradicular zone (afferent spinal reflex) (2) the fibers entering Clarke s column (afferent cerebellar system) (3) the fibers forming Goll s column

(afferent cerebral system) These three systems of fibers the integrity of which is essential for coordinate reflex progression and posture are affected always in tabes

Mott s observations led him to the conclusion that the degeneration of the exogenous systems of fibers was a spirochetal toxic primary dys trophy of the spinal protoneurons beginning in the collaterals and in tramedullary terminals and extending back to the ganglion cells in the posterior pinal ganglia and the degeneration of the peripheral nerve fibers is a later change It is assumed by the supporters of the peripheral origin of tabes that changes organic or functional in the sp nal ganglion cells might be due to neuritic or other processes in the peripheral nerve endings and this results in secondary degeneration of the posterior roots and the posterior columns of the cord Other pathologists seek to explain the origin of the tabetic process by inflammatory conditions of the meninges affecting the posterior roots Nageotte holds that in tabes there is a diffuse chronic meningitis which has all the characters of syphilitic origin namely infiltration with lymphocytes and plasma cells especially around the veins a meningomyelitic affection of the periphery of the cord medulla and even the cortex cerebri The escape of the anterior roots which is not found in syphilitic meningomyelitis was to Mott a fatal objection to Nageotte s theory

Redlich and Obersteiner maintain that at the point where the posterior roots penetrate the pia mater there is a constriction which constitutes a locus minoris resistentiae and that in consequence of meningeal inflamma tion and con triction as well as by thickening of the closely adherent blood vessels the po terior root fibers become as it were strangled Hence intramedullary degeneration occurs followed at a later stage by a retrograde degeneration of the extramedullary posterior root fibers The occurrence of degeneration elsewhere such as in the optic nerve ciliary ganglion and sympathetic system is a strong argument against the men ingitic theories

It is probable that the absence of the neurilemmal sheath of the intra medullary fibers together with other anatomical conditions viz the pecu liarities of the lymph circulation in the posterior columns pointed out by Pierre Marie and Guillain play some important part in rendering this por tion of the sensory protoneurons more susceptible to the action of the spirochetal toxin Homen and Orr and Rows have shown experimentally that toxins originating in the periphery ascend to the spinal cord more readily by the posterior than the anterior roots consequently in this way or by peculiarities in the lymph circulation the posterior roots and pos terior columns are more liable to damage

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psychosensory stimulation An Argyll Robertson pupil may be absent in some cases In 150 cases of tabes dorsalis Mott found it present on both sides in 73 5 per cent on one side only in 3 per cent in 15 per cent the pupils were inactive both to light and to accommodation convergence while in 3 7 per cent the pupils were very sluggish in their response to light

The Argyll Robertson pupil is so frequent being found generally in about three quarters of the cases and so characteristic that in its absence unless the other symptoms of tabes are very well marked it would be unsafe to make a diagnosis of this disorder apart from examination of the blood and cerebrospinal fluid Occasionally in tabes and more often in taboparesis and general paresis paradoxical reaction to light occurs viz on removal of the shading hand no reaction takes place for a second or two then the pupils dilate slightly Mobius thus explains the phenomenon probably during the process of covering the eyes the patient is accommodating and when the shading hand is removed accommodation is relaxed the process of accommodation being a slower process than the light reflex

A sluggish reaction to light is not necessarily pathological and unless there is a difference between it and accommodation it may be of no import An absent reflex to light occasionally is unilateral or one pupil may be more sluggish on one side than the other In a large proportion of cases the pupils are unequal and in a very considerable proportion they are smaller than normal They may be of medium size or even larger than normal on one or both sides The essential and characteristic feature is reflex iridoplegia and this when once complete is unalterable but occasionally when incomplete the full reaction may return The tabetic pupils rarely are quite circular and often one or both are irregular An Argyll Robertson pupil may exist for years without any other obvious sign of tabes or general paresis So rarely does it occur in any other disease than tabes and general paresis whether as a consequence of congenital or of acquired syphilis that a person having this sign and presenting no other symptoms may as Babinski has said be regarded as a candidate for one of these two forms of parenchymatous syphilis

Paralysis of the external ocular muscles also is common in tabes and one of the first symptoms which brings a tabetic patient under medical examination may be a squint and double vision thus not an inconsiderable proportion of cases are seen first by the oculist The paralysis may be transient lasting a few days or a few weeks and then disappearing There may be permanent paralysis complete or incomplete of a single nerve Any muscle may be affected but the external rectus is the muscle affected

The endogenous system of fibers of the posterior columns, both ascending and descending fibers, arise from cells situated at the base of the posterior cornua; they are of varying lengths and serve to associate the sensory segments of gray matter at various levels; they degenerate in the later stages of tabes.

Mott's observations showed that there is a decided relationship between the degree of affection of the endogenous systems of the posterior column and the degree of ataxia; moderate atrophy of the endogenous system occurring in persons who were well on in the second stage of tabes. All those with marked or very marked atrophy were in the advanced bed-ridden paralytic stage. All those in the early or preataxic stage showed no degeneration of the endogenous systems, although there was extensive atrophy of root fibers and especially of their intramedullary projections.

J. C. Roux attributed the anesthesia of the testicle, bladder, heart and trachea, as well as that of the stomach, to changes in the sympathetic chain and splanchnic nerves. He proposed to substitute for the formula "sclerosis of the posterior columns," "sclerosis of the posterior roots," as the primary basis of tabes. He thus inaugurated the radicular or root theory of tabes which is now entertained in one form or another by the majority of neuropathologists.

Symptomatology

The signs and symptoms of tabes are manifold, but the fundamental ones which are seldom absent are: (1) pupillary changes; (2) lightning pains; (3) absence of deep reflexes; (4) some visceral disturbance, especially bladder troubles; (5) disturbances of sensibility; (6) lymphocytosis of the cerebrospinal fluid; (7) usually a positive Wassermann reaction of the blood or fluid or both.

All these symptoms may be present as well as many others in the early stages of the disease and there may be no ataxia; in such cases the disease may be said to be in the preataxic stage.

Eye Symptoms

Pupil changes are met with in the great majority of cases of tabes and taboparesis. The loss of the reflex contraction of the pupils to light while it remains upon accommodation-convergence is the most valuable sign of tabes, taboparesis and general paresis; this is known as the Argyll Robertson pupil. The frequency of this sign was noted first by Erb as well as the usually associated loss of the reflex dilatation to sensory or

An important point to remember is the frequency with which optic atrophy is followed by general paresis in quite fifty per cent of the cases of this form of the disease met with in mental hospitals cerebral symptoms followed optic atrophy and blindness

Sensory Disturbances

Although there is a symptomatic similarity among all the cases by the more or less constant presence in some stage of the disease of certain sensory disturbances e g lightning pains anesthesia or analgesia there is hardly ever identity of symptoms and no two cases are exactly alike The complexity of the symptomatology agrees with the polymorphic character of the lesions A study of the microscopic changes in the peripheral and central nervous systems in a large number of these cases explains this general uniformity and special diversity of the symptom The fact that changes always occur in the posterior spinal roots and their projections in the cord explains the general uniformity in the objective and subjective sensory disturbances of the skin muscles and joint structures whilst the variability of distribution and extent of the morbid process in thirty two posterior roots and their projections in the cord as well as the variable degree of complication by lesions of the peripheral afferent nerves explains the frequent diversity of precise distribution and intensity of the anesthesia analgesia hyperesthesia and hyperalgesia met with The sensory dissociation shows that certain fibers subserving special functions are particularly affected e g the muscular sense fibers of the lower limbs and the nerve fibers innervating joint structures and bone again the light tactile anesthesia of the midthoracic region without analgesia shows that the disease process is selective and is related to the intraspinal terminations of the roots and not the peripheral nerves For in a neuritis the sensory symptoms have not this dissociation nor this distribution

There is a definite relationship between the degree of ataxia and the reflex spinal tonus which is due to partial or complete abolition of the intraspinal paths conducting afferent impressions from the muscles tendons and structures around and within the joints and the ataxia is due not only to the withdrawal of the guiding sensations but also to muscular hypotonus

Lancinating or Lightning Pains — The pain of tabes are variable in intensity situation and duration They are the earliest and most common subjective symptom and may indeed be the only one in slight and stationary cases The patient may have often suffered from them

most often A transient ptosis may precede an almost complete ophthalmoplegia or there may be a persistent paralysis of the levator palpebræ

Optic Tabes Atrophy of the optic nerve is one of the most serious symptoms that can arise in tabes it may be an early indeed a very early symptom and the defect of vision or blindness may be the first cause of the patient seeking advice its frequency is difficult to ascertain Gowers stated that optic atrophy occurred in 26 of 400 cases he had seen that is 6 5 per cent according to Voigt 1 in 14 cases suffers from optic atrophy according to Leimbach it may be the first symptom in 1 5 per cent The failure of vision usually begins with limitation of the peripheral field of vision in one eye and loss of color vision then the other eye becomes affected or both may be affected simultaneously The patients tell you frequently that they can see but it is like looking through smoked glass The onset and the course may be slowly progressive According to Dejerine the progress of the tabetic atrophy is rapid after from 6 to 18 months the blindness usually is complete An Argyll Robertson pupil usually is present and the dilatation of the pupil to pain is absent or diminished As blindness becomes more complete lightning pains are often less severe Sometimes the sight is lost apparently in a few days or almost suddenly Doubtless in some of these cases there has been loss of the peripheral field of vision with the retention of central acuity and it is the comparatively sudden destruction of the remaining fibers to the macula which leads the patient to believe he has lost his sight suddenly On examination of the fundus the disc has a pale or grayish appearance the vessels often being of normal appearance

The credit of first describing the form of tabes known as optic tabes usually is given to Benedikt who stated in 1881 that the abortive cases of tabes formes frustes are the ones in which optic atrophy is a prodromal symptom Gowers in 1879 however drew attention to the frequency with which ataxia does not come on when optic atrophy develops and he remarks in the fourth edition of his Manual and Atlas of Medical Ophthalmoscopy This fact was emphasized a few years later by Benedikt who disregarded the great frequency of early stationary tabes and enunciated a law that the development of optic atrophy tends to prevent the occurrence of ataxy Any so-called law easily obtains recognition however doubtful are the facts on which it rests Those which seem to support attract much more notice than those which do not

In 1887 Benedikt stated the law to which he knew no exception that tabetic motor symptoms no matter what development they may have reached vanish as soon as optic atrophy appears Dejerine pointed out that this latter statement is not true and all neurologists would agree

matter subserving painful sensation for this leg or the intraspinal terminals of the posterior spinal neurons had been completely destroyed therefore painful sensation could not be projected outwards into the limb

The pains may last during the whole course of the disease but frequently in the third stage of the disease when the roots have become completely destroyed the pains abate or cease that is if the disease does not steadily spread up to affect the arms

Paresthesia — Subjective sensations of various kinds as numbness pins and needles formication a cold trickling feeling in the skin a feeling in the soles of the feet of walking on putty wool or velvet may be complained of In rare cases Hutchinson s mask due to affection of the fifth nerve occurs The patient says his face feels stiff and he feels as if it were covered with a cobweb Paresthesia of the arms like the pains affects the postaxial border of the limb the distribution of the eighth cervical and first and second dorsal roots Consequently patients often complain of numbness and tingling in the ring or little fingers

Trunk anesthesia to light tactile impressions is the earliest and most constant objective sensory disturbance In most cases the affection is bilateral and symmetrical or nearly symmetrical both upper and lower borders forming a sharp horizontal line which corresponds to the zones of distribution of the roots In this zone of anesthesia to light tactile impressions there may be a zone of analgesia or hypalgesia or scattered points of blunted painful sensation The area of anesthesia or hypesthesia of the trunk usually was more considerable than the analgesia or hypalgesia The zone of hypesthesia or anesthesia occasionally is only unilateral or it may be asymmetrical extending over more segments on one side than the other The trunk anesthesia is met with most frequently in the fourth and fifth segments it may extend up the chest to the third or the second interspace and then the inner side of the arm also becomes affected This may extend to the whole inner side of the arm or only the inner side of the upper arm and forearm In the advanced cases there may be light tactile anesthesia continuous with the thoracic anesthesia affecting the whole inner half of the arm and corresponding to the distribution of the first and second dorsal and the seventh and eighth cervical segments that is the whole postaxial border of the limb It does not extend beyond the second intercostal space on the trunk because it is very seldom that the upper cervical roots which enter into the formation of the cervical plexus are affected

In 33 of 48 cases of tabes examined by Mott the legs were analgesic or hypalgesic There was usually complete insensibility to the prick of a needle or the feeling only of something touching below the knee in all

years before their true nature is discovered They may be slight or severe generally occurring in paroxysms and are likened to stabbing shooting boring lightning or to hot wires or the thrust of an electric needle into the flesh A patient may be free from pains for hours days weeks or even longer they may last a few minutes and then cease to recur again in the same situation or in another The attacks of pain may last a day a day and night or several days causing the patient the greatest suffering relief being obtained only by morphia Rarely does the pain correspond with the distribution of the nerve although a patient may come to the physician thinking he is suffering with sciatica The superficial pains seem to be on the surface or just beneath the surface They are felt usually at one spot often only a few inches in extent but may extend down part of a limb or affect the ear the face or the region of the mouth The pain usually is extremely brief a stab or flash of pain gone as soon as felt but recurring These superficial pains have one remarkable effect they make the skin tender The seat of the pain is most varied It may start in the great toe and the patient thinks he has gout it may start in the region of joints and be attributed to rheumatism or it may be felt in the skin or muscles The skin usually is hyperesthetic over the seat of the pain whether it be superficial or deep and this hyperesthesia may last after the pains have ceased Herpetic eruptions follow in rare instances such herpes differing from true zoster in tending to be recurrent In other patients erythematous patches may occur after an attack of pain When pain affects the trunk frequently it is unilateral and not uncommonly accompanied by gastric crisis The girdle pain frequently is experienced and a tightness compared to an iron jacket or the constriction of a tight belt is a frequent symptom The pain running down the inner side of the left arm might be mistaken for angina Very often the pains radiate all over the body and quite a number of patients who suffer with gastric crises say that with the attacks of vomiting pains start from the midthoracic region and radiate all over the body with the exception of the face Mott met with a case in which the face was unaffected except in an area which corresponded to the distribution of the second cervical root another a woman suffered so severely that she could hardly bear the touch of bed clothes and even the light of the windows was so painful she would bury her face in the pillow the only part of the body where she did not suffer the severe pains during these crises was the left leg below the knee The right leg had been amputated above the knee for Charcot s arthropathy The left leg in which the pains did not radiate was absolutely analgesic and anesthetic below the knee This would rather indicate that the sentient gray

touching with the tip of the finger generally appreciate heat and cold but very frequently a tube containing hot water can not be distinguished from that containing ice cold water and in advanced cases both may be said to have caused a pricking or burning sensation Delay in response is frequent in all forms of sensory disturbance This is generally in proportion to the intensity and extent of the anesthesia In advanced cases also if the patient feels the stimulus it is wrongly localized in the other limb sometimes in a similar position allochiria and in a few instances to a point of the skin above the next joint higher up in the limb A stimulus which is not felt at first subsequently may provoke a response by repeating it a few times thus illustrating the effect of summation A prick in one spot may be felt in many places polyesthesia on both legs

Postural Sense — Loss or impairment of sense is an important factor in the production of incoördination of movement and is associated usually but not necessarily with loss or disturbance of cutaneous sensibility The sense of position of the toes and fingers is usually affected first then of the ankle and wrists and later the more proximal joints this agrees with the distribution of objective sensory disturbances No doubt the protoneurons subserving cutaneous and postural sensibility are quite independent structures but as a rule they are affected simultaneously Arthropathies may occur without loss of postural sense and without ataxia but no cases are met with in which postural sense is much diminished or lost without ataxia being present

Ulnar Sensation of Biernacki — In many cases it is found that compression of the ulnar nerve at the elbow produced no tingling or pins and needles in the fingers it must however be remembered that in many normal people one cannot sufficiently compress the nerve to produce pain

Insensibility to Pressure of Testicles — In some cases pressure of the testicles produced this sign which undoubtedly is a useful one and is usually associated with impotence

Vibration Sense — A large tuning fork placed on the bone may cause no sensation of its vibration in tabetic patients especially in the legs indicating a break in the path of conduction of the sensory impulse from bone This sign is fairly constant in the ataxic stage of the disease in early cases (preataxic stage) vibration sense may be merely diminished

Visceral Disturbances

The especial frequency with which the midthoracic and lowest lumbar and sacral roots are affected in the early stages of tabes serves to explain the frequency of gastric crisis and bladder troubles

cases of tabes of the third stage and often also in the later portions of the second stage In a great many instances this analgesia was accompanied by light tactile anesthesia This anesthesia often was associated with genital perineal and anal anesthesia indicating involvement of the lower four sacral roots whereas the parts below the knee indicate fourth and fifth lumbar and first sacral Analgesia or hypalgesia of the lower extremities sometimes is limited to the sole of the foot or the peroneal surface of the lower part of the leg it may exist independently of trunk anesthesia and be the sole objective evidence of sensory disturbance A patient may show previously no cutaneous disturbance and then anesthesia or analgesia develops after several attacks of pain

Hyperesthesia and Hyperalgesia — An area in which pains have been experienced whether in the trunk or limbs may be hyperesthetic and precede anesthesia or analgesia it indicates the irritation prior to destruction of the root fibers or their intraspinal projections Very frequently an area may be hyperesthetic above or below a complete anesthetic or analgesic area A zone of hyperesthesia therefore is met with frequently above the third or fourth thoracic interspace or below the seventh or eighth Again there may be a patch of hyperesthesia situated within an anesthetic area or on one side of the trunk or in one limb there may be hyperesthesia or hyperalgesia while corresponding parts or nearly corresponding parts of skin on the other side may be anesthetic Systematic microscopic examination of the spinal cords and their roots serves to explain these facts Thus Mott found in fairly advanced cases of tabes a more complete degenerative fiber atrophy in the lumbosacral and middorsal regions than in the remaining segments of the cord Excepting when the arm was involved the degeneration of the roots ceased about the eighth or seventh cervical segments This explains also the fact of the distribution of the anesthesia The unequal affection of roots will not only account for cases where there is asymmetrical distribution of anesthesia and analgesia but also for hyperesthetic zones on one side with anesthetic on the other likewise a widespread distribution of anesthesia and analgesia in the midst of which are islands of varying size which are still sensitive to light tactile sensation or pricking of a pin may be accounted for by the fact that some of the posterior spinal neurons with their spinal projections and intraspinal terminals still are intact There is usually a gap in the regional distribution of anesthesia over the abdomen and thighs these skin areas are supplied by the lower dorsal and upper one or two lumbar roots and it is these roots which microscopic examination shows to be less affected

Thermoanesthesia — This is not met with nearly as often as affections of light tactile sensations Regions which are insensitive to pricking or

rupture of congested vessels The patients suffering with severe attacks are quite unable to retain food or even water in the stomach and the pains may be agonizing It is remarkable how soon they recover when the attack ceases Indeed it is not uncommon to find a patient enjoying a hearty meal a short time after the vomiting ceases Chemical analysis of the gastric secretion has given variable results but generally the acidity is diminished

Occasionally patients suffer with incomplete gastric crises in which there are merely paroxysms of cramp like pain of the stomach or only eructations and vomiting without pain Cases of gastric crises occasionally are accompanied with frequent purgations They are unaccompanied by pain apparently suddenly and without cause frequent watery evacuations of the bowels take place for days weeks or months and then cease as suddenly as they appeared Such crises occasionally occur without gastric symptoms and have been termed intestinal crises Rectal crises however are not so rare and are met with in about eight per cent of cases as with gastric crises they may be among the earlier symptoms The patients complain of tenesmus and urgent desire to defecate of severe pain in the rectum like the introduction of a hot iron sometimes this is accompanied by tenesmus and straining and more rarely evacuations of blood and mucus may be passed Much more frequently the patients suffer with constipation and difficulty in relieving the bowels without purgatives Not infrequently there is temporary incontinence This is especially the case when they have to start micturition by strong voluntary pressure of the abdominal muscles feces then are apt to escape owing to some loss of the reflex tonic contraction of the sphincter ani moreover they cannot always tell when defecation is complete Tabetic pruritus ani is sometimes an early symptom and generally paroxysmal

Laryngeal Symptoms —Laryngeal crises after those of the stomach are the most common crises and their characters vary considerably Graeffner in 226 cases of tabes observed paresis or paralysis of the vocal cords fifty four times Besides this he regards vocal cord tremor as an important sign of tabes because it occurs in no other organic disease of the nervous system to anything like the degree that it does in tabes This tremor is the rudimentary form of the laryngeal crisis and due to overaction of the adductors The commonest form of laryngeal crisis is due to adductor spasm overcoming the weaker abductor and the symptoms may resemble whooping cough or laryngismus stridulus There is a true laryngeal spasm with noisy inspiration and expiration cough and often marked dyspnea Gowers states That in one recorded case

Bladder troubles are among the earliest and most constant symptoms of tabes They are often not severe and the patient frequently fails to seek advice for this reason It is only as the result of inquiry as a rule that the patient in relating his symptoms mentions difficulties in starting micturition or holding urine When asked if he has noticed any difficulty with his water the patient will tell you either that he has a difficulty in starting the stream requiring a strong voluntary effort on his part or that it lacks force and takes him some time to empty the bladder In the later stages he does not empty the bladder completely consequently he frequently suffers with residual urine and catheterization may be necessary This condition indicates lack of power in the detrusor urinæ whereas another frequent condition met with indicates loss of reflex tonus in the sphincter for a cough laughing or any cause leading to increased intra abdominal pressure suffices to cause the escape of a little urine into the urethra followed by the urgent desire to micturate Imperfect contraction of the bladder even when not very pronounced may lead to serious complications for residual urine tends to decompose and gradually induces overdistention cystitis results and secondary infection of the kidneys may develop insidiously and even when difficulty of micturition has been apparently slight and therefore unheeded may lead to a fatal termination Slight intermittent febrile disturbances always should put one on guard concerning decomposition of residual urine

Vesical crises occasionally occur but they are rare They consist of violent pains which occur in the lower part of the abdomen radiating to the urethra and the inner side of the thighs The patients have an urgent desire to micturate but are unable to do so they experience the most severe burning and cutting pains in the urethra and these may be associated with lancinating pains throughout the lower extremities These crises may last a few or many hours

Gastric crises are among the frequent symptoms of the disease and sometimes the attacks of pain and vomiting are the sole cause for which the patient seeks relief The crises are associated with complete or partial anesthesia in the middorsal region and often with persistent subjective girdle sensation but by no means is every case of thoracic anesthesia associated with gastric crises

The attacks of vomiting may be preceded by a pain or a feeling of weight at the epigastrium Severe attacks may last several days the patient vomiting the contents of the stomach whatever they may be and the retching continuing with short intervals only mucus or watery mucus frequently mixed with bile being voided In severe cases the patients occasionally vomit coffee ground material or blood due probably to

crossed that is loss of knee jerk with retention of ankle jerk on one side and loss of ankle jerk with present knee jerk on the other side The loss of deep reflexes in the lower limbs may precede by years the appearance of ataxia

The triceps jerk is often lost when the knee jerk is absent although there might be no change in the other deep reflexes of the arm Occa sionally as Hughlings Jackson observed the knee jerk may reappear on the affected side after an attack of hemiplegia resulting from a cerebral vascular lesion Return of the knee jerk has been observed also on the side upon which a number of epileptiform convulsions occurred

Superficial Reflexes —The superficial reflexes are directly correlated with the skin sensibility consequently the abdominal and epigastric reflexes excepting in very advanced cases generally are present The plantar reflexes usually are diminished flexor in type and are unobtainable in some cases the cremasteric and gluteal reflexes are present more often than the plantar because the plantar surface next to the midthoracic region is more likely to have sensibility defective or abolished In the early stages of the disease there may be a considerable exaggeration of all the cutaneous reflexes

Muscle Tonus

A more or less marked diminution of muscular tone occurs in all cases of tabes dorsalis with the occasional exception of early cases in the pre ataxic stage There is usually a distinct relationship between the degree of hypotonus and the ataxia of the limbs and if there is a difference in the coordination of the two limbs it is observed that the hypotonus is more marked in the more ataxic limb The degree of loss of tone may be estimated by Franckel s method The patient is laid flat on the back on the bed and told to keep one leg on the bed fully extended in the healthy person in whom there is normal tone in the hamstring muscles the limb cannot be raised to a right angle with the body when there is impairment of the normal tone it can and in advanced cases of tabes especially when they have advanced to the bedridden stage the hypo tonus is so great in the hamstring muscles that the limb can be flexed at the hip to such a degree that the toes may be made to touch the forehead Another method of showing hypotonus is by keeping the knee flat on the bed with one hand and raising the foot with the other ac cording to the loss of tone the heel can be raised from the bed The sudden giving way of the legs not infrequently met with even early in the disease may be due to an exhaustion of the tonic contraction of muscles

the spasm spread to the pharynx making swallowing impossible a violent attack extended to the muscles of respiration and the patient died asphyxiated Death from these attacks is however very rare

Craeffner observed the interesting fact that the upper part of the trapezius was diminished in size in 25 cases out of 113 examined and 11 of these were associated with laryngeal paralysis and 4 with tremors These facts show an affection of the bulbar portion of the spinal accessory nucleus or nerves to account for the laryngeal paralysis and the wasting of the trapezius

Bronchial crises have been described as paroxysms of rough hard cough sometimes ending in a 'whoop such attacks of paroxysmal cough are more frequent than definite laryngeal spasm They frequently occur in the early stages of the disease but definite crises of laryngeal spasm may also be among the early symptoms and not infrequently they are associated with gastric crises

An increased frequency of the pulse rate is associated with laryngeal crisis and even anginal attacks have been described but arteriosclerosis aortic disease and aneurysm are not infrequent in tabes

Disturbances of Genital Organs — Impotence may be an early or a late symptom It may be preceded by satyriasis In some cases impotence is associated with anesthesia of the external genital organs and in other with atrophy of the testicles Diminished sexual power occurs in many cases and absolute loss of sexual power in about 20 per cent this too may be an early or late symptom Increased sexual desire is not uncommon in the early stages of taboparesis and is frequent in early general paresis

Satyriasis in a taboparalytic may be associated with delusions of extraordinary sexual power there is often marked desire but no ability to perform the sexual act Such patients may be taken up for indecent exposure and assaults on young children

Clitoris crises occasionally occur in female tabetics a patient of Mott s suffered with pruritus of the genitals and this led to her rubbing the parts causing painful erection of the clitoris

Deep and Superficial Reflexes

As Westphal first pointed out loss of the knee jerk is one of the earliest and most constant symptoms of tabes As a rule both knee and ankle jerks are absent In some cases the ankle jerks only are lost while in a small proportion of cases one or both knee jerks are absent the ankle jerks being retained Similarly the loss may be unilateral or

In advanced cases the joint surfaces with the cartilages may quite disappear and the bony structure in the joint may be destroyed and appear as eroded away Proceeding pari passu with the atrophy there may be numbers of outgrowths in the capsule and synovial membrane Chemical examination shows that the bones are deficient in mineral matter especially phosphates The Haversian canals are dilated irregularly and filled with fat According as the process affects the epiphysis or the diaphysis an arthropathy or spontaneous fracture occurs sometimes both Similar joint affections may occur in syringomyelia

A peculiar malformation arises when the joints of the tarsus are affected (tabetic foot) on the back of the foot and in the middle of the sole there arises a hard prominence the foot is flattened and shortened and the bones of the tarsus are as it were driven into one another Crepitus is obtained on movement but no pain produced The ligaments of the joints may be destroyed Tendinous tissue probably may undergo similar atrophic changes for sudden painless rupture of a tendon which does not tend to heal may occur

Whether the bone and joint disease of tabes is dependent upon a definite lesion of the nervous system still is uncertain Charcot believed at first that it was due to a lesion of the anterior horns while Virchow considered tabetic arthropathy as osteo arthritis occurring in a syphilitic subject Other authorities attribute it to a disease of the peripheral nerves especially of those supplying the bones but such joint lesions do not occur in peripheral neuritis

Ataxia Incoordination in Gait and Station

The characteristic ataxia develops gradually it is increased in the dark or on closing the eyes and at first may be present only when the visual guiding sense is absent Before the ataxic gait appears there may be a static ataxia and the patient notices that he sways and feels as if he would fall when closing his eyes to wash the face The early defect in coordination thus may be discovered by the patient or he may discover it by finding a difficulty in walking in the dark or ascending or descending stairs The incoordination of gait and station may be early symptoms but as a rule they do not occur until the disease is well established and after the patient has suffered for some time from lightning pains bladder troubles gastric crises or other symptoms Romberg s sign is the swaying and tendency to fall which is observed when a patient is made to stand with the feet together and the eyes shut the narrower the basis of support the more difficult does the patient find it to maintain his equilibrium.

One of the earliest paralytic signs of tabes is a loss of tone in the dorsal flexors of the foot and consequent foot drop while the patient is lying on his back in bed When such a patient is told to flex rapidly his hip to the uttermost it will be observed that the synergic dorsal flexion of the foot with hip and knee does not take place By the aid of vision and attention he can produce flexion but it involves continuous attention and even then it is not synergic but follows the flexion of the hip The hypotonus is due to the deficiency of afferent stimuli for all the muscles respond normally to faradism

Disturbances in the Bones and Joints

Arthropathy and bone affections occur relatively frequently in cases of tabes Spontaneous dislocation or fracture may be the cause of the patient seeking medical or surgical advice A joint affection may be the sole symptom causing the patient any trouble for of course the physical signs namely the Argyll Robertson pupils and absent knee jerks would be unknown to the patient and if there were lightning pains they would be put down to rheumatism There is no doubt that as in rheumatoid arthritis arduous occupations involving much use of the joints predispose to the disease

Symptoms — A masterly description by Charcot of the tabetic arthropathies has led to the affection being named after him He pointed out that without any sufficient cause a joint would suddenly swell up owing to a serous exudation into it and possibly into the surrounding tissues This swelling is unaccompanied by either pain or fever In the favorable form the swelling may disappear after a time and a return to the normal condition take place or severe destruction of the joint may occur accompanied by crepitus wearing away of the articular surfaces and even the bone causing dislocations and deformities The knee is the most frequently affected after this the hip shoulder elbow wrists more rarely the ankle vertebral and finger joints Marie considered that from 4 to 5 per cent of tabetics suffer from joint affections When incoordination is associated with the arthropathy the varying strain on the ligaments and tendons necessary to maintain the erect posture coupled with the hypotonus of the muscles may lead to retroflexion of the knee joints

Radiographic examination shows absorption of the articular surfaces of the bones and disintegration of the joint

Pathological Anatomy — The capsules and synovial membrane are thickened contain excess of synovial fluid and the cartilages are ulcerated

asked to hold his hands out and bring the tips of the fingers of the two in apposition As it increases all movements are performed with uncertainty thus the patient may find it difficult to unbutton and button up his trousers before and after micturition and this may lead to his bladder becoming distended

The grasp is not sustained first one finger relaxes and then another Occasionally the trunk muscles present signs of incoordination thus a patient may be able to sit steadily on a chair with his eyes open but if he closed them would at once fall off It is remarkable that the movements of the head face and eyes escape the characteristic derangements (Gowers)

Muscular wasting with degenerative changes is rare Atrophy of the small muscles of the hands may occur and is the result of degenerative changes in the anterior horn cells of the corresponding segments of the lower cervical region of the spinal cord (atrophic type of tabes)

In the paralytic bedridden stage there is great muscular wasting and there may be a great amount of loss of tissue of the abdominal muscles so that when the diaphragm descends in inspiration the flaccid abdomen is ballooned out Again the abdomen may be retracted and owing to atrophy of the quadratus lumborum and oblique muscles the lower ribs are drawn in on contraction of the diaphragm and a groove is formed

Cranial Nerve Affections

Although loss of smell and the taste for flavors is met with rarely in tabes it is met with occasionally in taboparesis and general paresis

Sometimes the patients are said to lose sensibility of the mucous membrane of the nose and no longer sneeze when it is irritated or they may be subject to paroxysmal attacks of sneezing and tickling of the nasal mucous membrane This is due to affection of the nasal branch of the fifth nerve and is rare Other affections of branches of the fifth nerve are pains anesthesia and parasthesia in various regions of its distribution Besides these disturbances of sensibility there may be various so called trophic disturbances such as a rapid falling out of the teeth and absorption of the alveolus of the jaw

Other rare conditions due to affection of the trigeminal nerve have been described viz *ophthalmia neuroparalytica and corneal ulcer* Both corneal ulcer and tabetic ulcer of the mouth are analogous to the perforating ulcer of the foot Again sialorrhea which occasionally occurs generally in paroxysmal attacks has been attributed to affection of the fifth nerve Quite exceptionally the motor root of the fifth is involved

therefore he cannot stand on one foot The effect of removal of the visual guiding sensation is more pronounced when the patient has lost sensibility in the soles of the feet but it does not wholly depend upon this loss of sensibility for swaying may be marked when the sensation of the soles of the feet is perfect The difficulty often is noticed to be greater when the feet are bare this is because muscular action has to supplement the support which the boot usually affords The patient may sway from side to side or from toes to heels The uncertainty of gait and station progresses and it becomes noticeable even with full visual guidance especially on uneven ground going up and down stairs or on a smooth surface A slight visible alteration in walking is observable there is a change in the mode in which the feet are placed on the ground there is a noticeable difficulty in turning round suddenly and he stamps the foot down to prevent falling As the muscular incoordination and hypotonus increase the change in gait becomes greater but naturally this change varies in precise characters according to the roots affected The patient after a time walks with a noticeably wide base and finds it necessary to use a stick to increase the base of support the feet are raised too high thrown forwards too far and brought down suddenly with a stamping action it may be necessary even to have a supporting arm although only a slight degree of help is necessary at first for it is guidance and the feeling that he will not be allowed to fall which is so needful Later the incoordination may be so great as to necessitate a stick in one hand and the support of an arm on the other the legs being thrown out in such a jerky incoordinate manner even when guided by vision that he would be unable to stand or walk without such support Eventually he may be unable to stand even with help for when attempts are made to rise the wasted limbs are jerked about in such an irregular incoordinate manner that he is unable to assume the upright position and if he succeeds in so doing owing to the atrophy hypotonus and incoordination they refuse to support the body and slip away forwards in front of him only the strong support of an attendant preventing him from falling The incoordination also is observable when the patient is lying in bed for if he is asked to try and touch an object with his foot the leg is thrown wide of the mark and the incoordination is more marked when the eyes are closed

As a rule the arms are affected much later than the legs and not infrequently there is no incoordination of movement observable in them Occasionally but rarely the arms are affected first (brachial tabes) This defect usually is revealed first in the finer movements of the hand such as in writing It may be tested by telling the patient to touch some object with his eyes closed such as the tip of his nose or he may be

Cerebral Symptoms in Tabes and Taboparesis

Mental symptoms developing in a patient with tabes dorsalis usually indicates the onset of paresis degenerative encephalitis and thus converts the case into one of taboparesis it should be remembered however that in a few cases of tabes the mental symptoms may result from a supervening attack of one or other of the phases of a manic depressive psychosis A few cases of tabes suffer from suicidal impulses the result of a psychotic depression precipitated by constant lightning pains and the knowledge or belief that they are suffering from an incurable disease

It seems a well-established fact that some cases of tabes with developed and well pronounced mental symptoms and without treatment of any kind may become less ataxic with an improved gait On the other hand a few cases admitted to a mental hospital for an attack of mania or other indications of general paresis without previous symptoms of tabes will develop progressive ataxia subsequently

As in general paresis so in taboparesis the onset of cerebral symptoms may occur suddenly with seizures which are recognised as congestive apoplectiform and epileptiform The seizure may lead to a disturbance of consciousness or partial or complete loss of consciousness Thus a patient may be suffering from discovered or undiscovered symptoms and signs of tabes dorsalis when suddenly he is seized with some kind of fit There may be a temporary disturbance of consciousness a sudden feeling of giddiness associated with frontal headache Generally such an attack is due to circulatory disturbances of the brain but it is conceivable that in rare cases of tabes frequent migrainous attacks may be due to disturbances of the sensory impressions from the semicircular canals These attacks often escape observation until one more severe necessitates a doctor's advice when the true nature of the disease may be discovered by the examination of the pupils and the condition of the knee jerks and other signs of tabes or taboparesis Epileptiform seizures may be the first evidence of cerebral affection and may precede or succeed spinal symptoms It is estimated that epileptiform seizures occur in 30 per cent of cases of taboparesis

Individuals with an inherent psychopathic disposition may quite apart from organic changes in the brain develop *systematized* delusions of persecution and put insane interpretations upon the pains and visceral crises These delusions often are accompanied by hallucinations both auditory and visual Mott observed that patients with optic atrophy were particularly liable to develop visual hallucinations In 28 per cent of mental hospital cases of tabes the patients were affected with delusions

Disturbances of taste are very rare cases do occur occasionally in the form known as medullary tabes

The auditory nerve is affected only rarely the lesion may be irritative or paralytic Paroxysmal attacks of noises in the ear like rushing water bells shrill whistling sounds or even musical sounds may be heard This no doubt is due to affection of the cochlear branch of the auditory nerve but the neurons supplying the semicircular canals may in rare cases be affected also and give rise to symptoms of Meniere s syndrome viz, attacks of vertigo and loss of balance and occasionally vomiting

Symptoms pointing to affection of the vagus may occur viz an habitual acceleration of the pulse rate heart crises have been described also in which there is a violent precordial pain radiating to the shoulders especially the left with a feeling of oppression and during the attack tachycardia and arrhythmia a condition similar to angina pectoris Cardiac syphilis however not infrequently is met with in tabes consequently such attacks may be due partly to the same cause as true angina pectoris as there is always the possibility of sclerosed coronary arteries

The hypoglossal nerve also is not immune for cases have been recorded of unilateral atrophy of the tongue Very rarely is it bilateral The cranial nerve symptoms often occur in groups

Vasomotor and Trophic Disturbances

Several conditions already mentioned may be regarded as trophic disturbances due to the changes in the sensory protoneurons but one of the most striking illustrations of trophic change is afforded by perforating ulcer This condition has been found to be almost confined to tabes it may begin in a corn the most frequent situation is the sole of the foot or one of the toes more often the great toe it may be on the back of the toe It is a suppurative process owing to deep seated mischief which bores through the skin frequently there is carious bone at the bottom of the fistula from which a little foul pus escapes continually These ulcers are painless and very difficult to heal Local sweating has been observed confined to the soles and palms or to one side of the head Herpes occasionally occurs usually in association with an attack of pain and has a tendency to recur The growth of the nails may be affected those of the feet and sometimes those of the hands may become thickened and furrowed or show irregularity of their surface or the nails may fall off and only slowly be renewed Ecchymosis of the skin and changes in the growth of the hair in connection with attacks of pain have been reported The pigment may disappear from the skin and hair in patches

cially of the right of the first part of the aorta on x ray examination (3) in the electrocardiogram abnormalities such as widening of the QRS complex and flattening or inversion of the T wave especially in the first lead

Course and Termination

The disease usually runs a chronic course it extends on an average over a period of ten years but the duration may be as long as twenty or thirty years and even more A patient rarely dies within a few years of the onset of symptoms Case have been known to remain for twenty years or more in the preataxic stage on the other hand the patient in a short time after the onset of definite symptoms becomes helpless and bedridden from rapid progress of the ataxia

The onset of the symptoms or the rapid progress of the disease may follow exposure to cold and wet or falls and injuries still more common is a rapid increase of the symptoms in consequence of alcoholism Cases are met with in which symptoms of tabes have appeared after an attack of malaria influenza and other diseases One of the commonest causes of aggravation of the symptoms and one fraught with danger is due to residual urine in the bladder undergoing decomposition and causing cystitis which subsequently leads to an infective pyelonephritis Too much care cannot be taken to avoid this serious complication and it is well to remember that this is a common cause of a remittent pyrexia

The course of the symptoms is most variable in some the pains are so severe as to be the principal subjective sign of the disease Periods in which the disease is apparently stationary for months or years may alternate with exacerbations for which one of the causes mentioned above may be elicited or they may be apparently spontaneous with no discoverable exciting cause In most cases there is nothing in the nature of the disease itself to cause death The cause of alarming symptoms is laryngeal paralysis or spasm and occasionally owing to this cause the disease per se occasionally may prove fatal Although gastric crises are most alarming and lead to great prostration they are never fatal One cause of death is suicide or misadventure from taking drugs to relieve the pains Death often results from intercurrent diseases from fractures ending in suppuration and from bedsores By far the most common cause as previously stated is pyelonephritis the result of cystitis Bronchopneumonia also is a frequent cause of death In rare cases there may be a general muscular wasting Ten per cent at least of cases of tabes dorsalis develop dementia paralytica which may eventually prove fatal

of persecution poisoning electricity etc In three fourths of them there were either auditory or visual hallucinations often the two combined and the majority had a family history of mental disturbance The delusions of persecution associated with electricity in the body the poisoning of food twisting of the bowels withdrawal of the semen (impotence) bad smells and tastes have an organic basis in a patient suffering with tabes but when the patient associates those pains with the voice he hears of some particular individual who follows him day and night to persecute him and if there is no dementia it is probable we are dealing with a paranoiac who is also the subject of tabes According to Mott s experience delusions of persecution especially if systematized point more to tabes associated with inherent insanity than taboparalysis Grandiose delusions with exaltation very frequently supervene in a tabetic who develops paretic symptoms

A tabetic patient with mental symptoms who has the knee jerk absent on one side and present on the other or who gives a history of epileptiform apoplectic or congestive attacks is in all probability a taboparetic

Cardiac Symptoms

It has been pointed out already that pseudoanginal symptoms may occur in tabes and Mott recorded a case of laryngeal crises which was for some time thought to be laryngeal paralysis due to the pressure of a small deep seated aneurysm Berger and Rosenbach were the first to draw attention to the relative frequency of the coincidence of tabes and aortic insufficiency Ruge and Huttner found in 138 cases of tabes heart failure twelve times and marked aortic insufficiency nine times Fuslin described 17 cases of tabes with aortic insufficiency and Schuster 3 cases out of 22 cases of tabes while Lesser found an aneurysm in 18 cases out of 96 cases of tabes

A perusal of the literature indicated that clinical evidence of syphilis of the cardiovascular system has been found in some 30 per cent of cases of neurosyphilis while post mortem signs have been observed in over 50 per cent Bach and Worster Drought however found that in cases of parenchymatous neurosyphilis relatively few (8 per cent) showed definite clinical evidence of cardiovascular disease even with the use of modern instrumental methods (electrocardiography etc) Similarly relatively few cases of cardiovascular syphilis (16 per cent) showed clinical signs of neurosyphilis They considered that early signs suggesting a diagnosis of syphilitic aortitis were (1) accentuation of the second (aortic) sound (2) enlargement of the left and a slight fulness espe

TREATMENT

As the syphilitic organism is the essential cause of the disease the only therapeutic measures likely to arrest its progress are the administration of arsenobenzol compounds bismuth or mercury and iodide of potassium In general treatment should be on the same lines as described in Chapter XIX of this volume and Chapter XXVIII Part II of Vol V Following two or three years treatment and provided some relief of symptoms has occurred two or three courses of six injections each of neoarsphenamine and bismuth can be given each year the serological reactions of the blood and cerebrospinal fluid being determined from time to time As regards the arsenobenzol preparation used in treatment neoarsphenamine probably is as good as any other Some prefer silver salvarsan believing that it has more penetrative power in neurosyphilis while in the writer's experience acetylarsan (diethylamine acetarsone) has proved quite efficacious Tryparsamid is advocated by other observers

It is doubtful if intrathecal medication is at all superior to intravenous arsenobenzol in the treatment of tabes dorsalis The Swift Ellis treatment of injecting salvarsanised serum intrathecally may be reserved for cases with severe gastric crises or severe lightning pains who do not respond to the ordinary courses of neoarsphenamine intravenously and bismuth intramuscularly Mercurialised serum (a small quantity of mercury albuminate in 30 c c of horse serum) has been used intrathecally also the injection being repeated three or four times at fortnightly intervals Each injection gives rise to a fairly severe reaction in the form of generalised pain and often pyrexia If the patient is prepared to put up with these immediate effects the ultimate result often is good Again however this form of treatment should be reserved for cases that are not progressing under the more usual method of treatment

Induced malarial infection has been advocated also and applied to the treatment of tabes dorsalis The results however are very far from being so successful as in many cases of general paresis While few benefit others are rendered permanently worse by the series of malarial rigors The same may be said of other forms of induced fever including electro pyrexia

As regards general measures the patient should be warned that it is essential for him to lead a very steady quiet and simple life Care should be taken to avoid the risk of falls exposure to cold and wet if practicable he would do well to reside during the winter in a warm and equable climate A light and easily digestible diet should be ordered

A large proportion of these taboparetics suffer with optic atrophy it is not safe therefore to assert a long duration of life when optic atrophy leads to blindness

Syphilitic tertiary lesions of the skin and viscera are not common nor is syphilitic endarteritis affecting the cerebral vessels but arteriosclerosis aneurysm and valvular disease especially aortic disease are relatively frequent in tabes The presence of these conditions is more than coincidence for they have a causal relationship to syphilis also it is well to remember that a true angina pectoris from sclerosed coronary arteries may arise in a tabetic patient and that the characteristic pain may be wrongly attributed to the tabes A certain number of patients die of pulmonary tuberculosis but this is not nearly so frequent a complication as in general paresis

Prognosis

The prognosis in tabes largely depends upon the stage in which it is first detected and the life and habits of the patient subsequently Arrest of the symptoms is not infrequent and considerable improvement is by no means rare When the disease has advanced to the ataxic stage there is less hope of arrest but even then in some cases considerable improvement may be obtained under the influence of treatment Some cases of pseudo tabes really diffuse syphilitic spinal meningitis with symptoms resembling the true tabes undoubtedly clear up in a remarkable manner under antisyphilitic treatment but these are not examples of true tabes dorsalis Probably these are the cases of acute onset that have been recorded as recovering

Each attack of pain indicates irritation prior to degeneration of root fibers and the knee jerks may disappear after an attack of lightning pains lasting some days The occurrence of optic atrophy sometimes is followed by arrest of the symptoms in other parts and as Benedikt first pointed out such patients frequently remain for several years in the preataxic stage One of Mott s patients was a teacher of the blind and it was not until 24 years after he lost his sight and when he was over 50 that he developed ataxia Another patient developed ataxic symptoms at 65 and when he was 72 he was still in the preataxic stage The statistics of Marie and Moquet show that although tabes weakens the individual it does not on the whole materially shorten life Thus of 66 tabetic patients who died at Bicetre 51 5 per cent were over 60 years of age and 83 3 per cent were over 50 years of age Of 58 still living 43 per cent were over 55 and 68 9 per cent were over 50 years of age

few physicians may consider it desirable to prohibit tobacco one must agree with Byrom Bramwell s aphorism Smoking in moderation does not injuriou ly affect the busy man who thinks it only hurts the lazy man who drinks

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and any digestive disturbance or constipation should receive attention especially as these latter conditions tend to aggravate gastric crises and lightning pains Only a small quantity of alcohol preferably in the form of light wines should be permitted

A certain amount of muscular exercise is beneficial but the patient should be warned against over fatigue and any undue exertion that would result in exhaustion Frenckel s exercises which depend upon making full use of the vision to compensate for the defective postural sense are of benefit in ataxic cases

For lightning pains barbital (veronal) or aminopyrine (pyramidon) in doses of from gr 5 to 8 (0 3 to 0 5 gm) may be prescribed Veramon or peralga claimed to be amidopyrine diethylbarbiturate (Schering and Glatz) gr 6–12 (0 3 to 0 6 gm) sometimes is useful also as well as antipyrine (phenazone) Mercury salicyl arsenate (enesol) gr 1 (60 mgm) in a 30 minims (2 c c) ampoule given hypodermically may relieve an attack of such pains In many cases however morphia up to gr 1/3 (20 mgm) will be necessary it may be given in combination with gr $\frac{1}{100}$ (0 6 mgm) of atropine or hyoscine

Gastric and other crises sometimes will be relieved by chloretone gr 10 (0 6 gm) given every three hours while an initial dose of gr 20 (1 3 gm) may abort an attack Hyoscyamous in combination with belladonna also is useful as well as veramon (amidopyrine diethylbarbiturate) Morphia however frequently will be necessary Section of the posterior spinal nerve roots has been carried out by Foerster and others for the relief of both gastric crises and lightning pains but the results are of no permanent value In severe and obstinate cases more favourable results according to Symonds have followed section of the pain tracts in the spinal cord

If bladder trouble arises and residual urine with cystitis develop the treatment should be as described in the previous chapter It is very important to warn the patient against distension of the bladder he should never allow it to become over full as this tends to produce atony and residual urine It is best to encourage micturition at three or four regular intervals during the day

Mental anxiety worry and anything which causes mental depression have a prejudicial effect upon the nervous system in this as in all chronic nervous diseases in many cases however it is impossible to prevent the causes of mental stress especially in one suffering from a slow insidious and often painful and incapacitating disease

Should smoking be prohibited? Smoking is a solace to the mind of many men and it is a great hardship to give up their pipes Although a

PATHOLOGY

Macroscopic — Macroscopic changes are found in all cases except when death results in the acute stage of the disease The cranial vault usually is normal but there may be thickening of the bone with disappearance of diploe and adherence of the underlying dura The dura is slightly thickened In some cases there is a thick clot or neomembrane beneath the dura This is not an integral part of the disease but is due to extravasation of blood into the subdural space secondary to trauma This so-called chronic hypertrophic pacchymeningitis was formerly a common finding but with better care of these patients it has become a rarity When the dura is removed the brain is seen to be shrunken This loss of substance usually equal to 100 grams or more is due to atrophy of the brain which has a characteristic distribution. The atrophy is greatest in the anterior portion of the brain and progressively diminishes in severity toward the occipital lobe The frontal pole the dorsal surface of the frontal lobes and the tips of the temporal lobes are affected most severely The motor the sensory the parietal and the occipital cortices are spared usually except in the unusual cases of the so-called Lissauer s type where there may be a selective involvement of these areas

TABLE I

PATHOLOGY OF PARETIC NEUROSYPHILIS

MACROSCOPIC

1 Thickened and opaque meninges
2 Cerebral atrophy with { widening of sulci and dilatation of ventricles }
3 Granular ependymitis

MICROSCOPIC

1 Meningeal and perivascular infiltration (lymphocytes and plasma cell)
2 Proliferation of endothelial cells of the blood vessels
3 Loss of and degenerative changes in the nerve cells axis cylinders and myelin sheaths
4 Proliferation of microglia (rod cells) and macroglia
5 Deposition of iron pigment
6 Presence of spirochetes

The meninges over the atrophic areas appear cloudy and thickened (Figure 1) and the dilated subarachnoid spaces are filled with cerebrospinal fluid The meninges are adherent to underlying brain tissue and small pieces of cortex are torn away when an attempt is made to remove the leptomeninges On sectioning the atrophic portion is hard due to gliosis and there is dilatation of the lateral

Definition — Dementia paralytica is a chronic spirochetal meningoencephalitis which is characterized by a progressive deterioration of mental and physical capacities and death The inflammatory and degenerative changes in the brain are most severe in the anterior portion of the frontal and temporal lobes and become progressively less severe in the posterior portions of the hemispheres The disease has been variously designated as general paralysis of the insane, general paresis syphilitic meningoencephalitis and paretic neurosyphilis

Historical

Haslam[1] in 1798 described paralytic insanity' and in the next few years the disease was established as a clinical entity through the studies of Esquirol and Calmeil[3] Bayle[4] in 1822 described thickening and clouding of the leptomeninges, adhesions between the meninges and the cerebral cortex, internal hydrocephalus and ependymal granulations and correlated these findings with the clinical picture Delage[5] in 1824 was the first to use the term general paralysis, to describe the disease and two years later Calmeil[3] referred to it as ' paralysie generale des aliénés' The syphilitic nature of the disease was known to Esmarch and Jessen[6] long before the introduction of serological tests and the discovery of spirochetes The classic studies of Alzheimer[7] and Nissl[8] in 1904 gave all of the pathological features of the disease with the exception of the presence of spirochetes which were demonstrated by Noguchi and Moore[9] in 1913 and the characteristic distribution of iron pigment (Bonfiglio[10], 1911) The demonstration of spirochetes in the brains of these patients and the application of Wassermann s test to the cerebrospinal fluid by Plaut[11] in 1909 established beyond doubt the syphilitic etiology of the disease and led to the discard of the concepts of metasyphilis and parasyphilis Coincidental with the pathological and serological studies were the clinical studies of Kraepelin[12] His thorough analysis of the symptomatology and clinical forms of the disease left very little to be added by other workers

PATHOLOGY

Macroscopic — Macroscopic changes are found in all cases except when death results in the acute stage of the disease. The cranial vault usually is normal but there may be thickening of the bone with disappearance of diploe and adherence of the underlying dura. The dura is slightly thickened. In some cases there is a thick clot or neomembrane beneath the dura. This is not an integral part of the disease but is due to extravasation of blood into the subdural space secondary to trauma. This so-called chronic hypertrophic pacchymeningitis was formerly a common finding but with better care of these patients it has become a rarity. When the dura is removed the brain is seen to be shrunken. This loss of substance usually equal to 100 grams or more is due to atrophy of the brain which has a characteristic distribution. The atrophy is greatest in the anterior portion of the brain and progressively diminishes in severity toward the occipital lobe. The frontal pole, the dorsal surface of the frontal lobes and the tips of the temporal lobes are affected most severely. The motor, the sensory, the parietal and the occipital cortices are spared usually except in the unusual cases of the so-called Lissauer's type where there may be a selective involvement of these areas.

TABLE I

PATHOLOGY OF PARETIC NEUROSYPHILIS

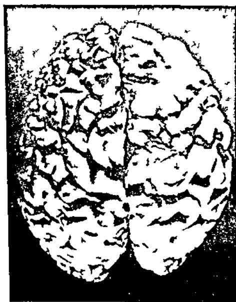
MACROSCOPIC

1. Thickened and opaque meninges
2. Cerebral atrophy with { widening of sulci and dilatation of ventricles }
3. Granular ependymitis

MICROSCOPIC

1. Meningeal and perivascular infiltration (lymphocytes and plasma cells)
2. Proliferation of endothelial cell of the blood vessels
3. Loss of and degenerative changes in the nerve cells, axis cylinders and myelin sheaths
4. Proliferation of microglia (rod cells) and macroglia
5. Deposition of iron pigment
6. Presence of spirochetes

The meninges over the atrophic areas appear cloudy and thickened (Figure 1) and the dilated subarachnoid spaces are filled with cerebrospinal fluid. The meninges are adherent to underlying brain tissue and small pieces of cortex are torn away when an attempt is made to remove the leptomeninges. On sectioning the atrophic portion is hard due to gliosis and there is dilatation of the lateral



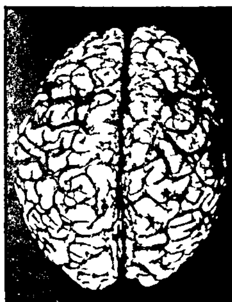


Fig 1 (a) Paretic Neurosyphilis Note cloudy and thickened leptomeninges and atrophy of cortex as shown by widening of the sulci (b) Normal brain on right side of figure

Fig 2 Paretic Neurosyphilis Frontal section of cerebral hemisphere There is advanced atrophy of the cerebral substance as shown by greatly enlarged ventricles and widening of the sulci

ventricles (Figure) and to a lesser extent of the third and fourth ventricles The surfaces of the ventricles particularly the fourth are covered by fine sand like granulations These ependymal granulations (Figure 3) are due to proliferation of the subependymal glia They are one of the most constant of the



FIG 3 High power view of the floor of the enlarged ventricles of cerebral hemisphere of Figure 2 Note sand like granulations (granular ependymitis) on the walls of the ventricles and thinning of the septum pellucidum

macroscopic findings and while not pathognomonic of dementia paralytica they are rarely present in any other condition which could be confused with it The blood vessels at the base are normal and there are no circumscribed areas of brain destruction or softening unless the case is complicated by arteriosclerosis The cerebellum brain stem and spinal cord usually appear grossly normal However the posterior columns of the cord may appear shrunken and grayish if tabes dorsalis is also present in which case one speaks of tabo-paresis

Microscopic — The microscopic pathology of dementia paralytica is characterized by *1) inflammatory reaction in the meninges and in the perivascular* spaces of the brain and spinal cord 2) proliferation of the endothelial cells of the blood vessels 3) degenerative changes in the parenchymatous tissues including nerve cells axones and myelin sheaths 4) proliferation of the microglia and macroglia 5) abnormal deposits of iron pigment and 6) the presence of spirochetes

Inflammatory Reaction — The meninges of the entire brain and spinal cord are infiltrated with lymphocytes and plasma cells (Figure 4) and there is an increase in the number of macrophages and fibroblasts The intensity of the



FIG 4 Nissl stain of cerebral cortex showing inflammatory reaction in the meninges in the perivascular spaces and in the cerebral substances There is a loss of nerve cells and a prolifera tion of the microglia

meningeal infiltration parallels the degree of cortical atrophy and is most intense in the frontal portion of the brain In some cases the meninges over the occipital lobe and cerebellum may be entirely free of exudate Similarly in the substance of the brain the perivascular infiltration is greatest in the atrophic areas The exudate is composed chiefly of plasma cells with occasional lymphocytes and microglial cells In most instances these cells are confined to the perivascular or Virchow Robin spaces but occasionally when the inflammatory reaction is un usually intense plasma cells and lymphocytes will be found lying free in the parenchyma

Changes in the Blood Vessels — In addition to the perivascular ' cuffing there are proliferative changes in the endothelial cells of the smaller capillaries and venules This varies from a mild swelling of the endothelial cells to a marked

degree of swelling and proliferation of these cells so that the lumen of the vessel appears narrowed or occluded On superficial examination there is an apparent increase in the number of blood vessels This is due to the fact that infiltrated vessels stand out prominently in the shrunken cortex In silver stains new capillary formation can be seen but in other special stains such as the Le Pehne Pickworth it can be seen that there is an actual decrease in the number of functioning capillaries

Parenchymatous Degeneration —Degenerative changes are greatest in the areas which are grossly shrunken In these areas there is a general reduction in the number of nerve cells and various degenerative changes in many of the remaining neurones The loss of nerve cells together with proliferation of glial cells leads to a loss of the orderly arrangement of cells into layers In some cases especially in juvenile or Lissauer s paresis there may be a laminar or pseudolaminar loss of nerve cells and status spongiosus of certain areas of the cortex With myelin stains it can be seen that there is a loss of myelin in the cortex and white matter and occasionally there are discrete patches of myelin loss such as is commonly found in multiple sclerosis With destruction of the myelin sheaths there is a concomitant degeneration of the axis cylinders but occasionally there may be myelin loss with preservation of the axis cylinders Secondary degeneration of the long tracts particularly the cortical spinal tract can be found in advanced cases and degeneration of the posterior columns is present in the cases of tabo-paresis and to a lesser degree in some cases where no clinical evidence of tabes is noted The optic and less often other cranial nerves may show inflammatory and degenerative changes

Neuroglial Reaction —The microglia cells proliferate and while they may assume any form they quite constantly become elongated into the so-called rod cells These cells are arranged parallel to the axis of the cortex and are so numerous that the resulting picture in Nissl or Hortega stain is highly characteristic Other forms of microglia including the comma-shaped and macrophages are found The latter are especially numerous when the degenerative process is rapidly progressive In special stains the presence of lipoids iron pigments and spirochetes can be demonstrated in the microglial cells Proliferation of the macroglia follows the loss of nervous tissue Gliosis especially in the subpial and in the subependymal region can be demonstrated by special stains The subependymal gliosis leads to nodule formation beneath the ependymal lining and produces the ependymal granulations which can be seen with the naked eye (Fig 3)

Iron Pigment —The presence of iron pigment in dementia paralytica was noted by Bonfiglio[10] in 1911 Later Hayashi[13] Lubarsch[14] and Spatz[15] stressed the value of this finding as a histological characteristic of the disease Spatz[15] devised a simple method by which a definite diagnosis of dementia paralytica can be made in a few minutes at necropsy or at operation A small specimen of cortical

tissue is washed rapidly in normal saline and allowed to stand 15 minutes in a concentrated solution of ammonium sulphide It is then transferred with glass instruments to normal saline A small piece is placed on a glass slide and pressed down with a cover glass The presence of small black dots globules of iron in the walls of the blood vessels is considered diagnostic of dementia paralytica In alcohol fixed material stained by the Turnbull blue method spicules of iron pigment are found in the walls of the blood vessels in the microglial cells chiefly in the rod cells and occasionally in astrocytes This type of iron pigment is not found in normal brain tissue and differs from that found after hemorrhage and softening In general the distribution of iron pigment in dementia paralytica parallels the inflammatory reaction The iron pigment gradually disappears in treated cases but persists longer than the inflammatory reaction

Spirochetes — There were many unsuccessful attempts to find spirochetes in the brains of patients dying of dementia paralytica before the report of Noguchi and Moore[9] in 1913 In their original study of 70 cases they found spirochetes in the brains of 12 In a later series of 200 cases Noguchi[16] was able to demonstrate them in 48 Since these reports other investigators have found spirochetes in a certain percentage but never in 100 per cent of their cases Jahnel[17] believes that there are cyclic increases in the number of spirochetes and the percentage of positive findings depends on the relationship of death to these cyclic increases Other factors such as the type of treatment prior to death and the diligence of the search are important also The failure to find spirochetes does not offer any serious diagnostic difficulty since the total histological picture otherwise is so characteristic

In sections stained by the methods of Jahnel Levaditi Steiner, Dieterle etc spirochetes may be found diffusely scattered through the brain (Figure 5) or in sharply demarcated nests which sometimes are visible to the naked eye Spirochetes are most numerous in the gray matter are occasionally found in the meninges but are almost never in the white matter They are found lying free in the gray matter, in the walls or lumen of blood vessels and in microglial cells but according to Jahnel they do not invade nerve cells The organisms are most numerous in the areas of the cerebral cortex which are the site of inflammatory and degenerative changes The number and distribution of the spirochetes have no relationship to the clinical picture Some authors have reported that they were more numerous in the expansive the rapidly advancing and in the cases with many convulsive seizures before death They are rare in the stationary cases and in the so-called Lissauer s type Spirochetes are rarely found if the patient dies soon after receiving proper antisyphilitic treatment

Pathogenesis of Lesions — The pathogenesis of the lesions in dementia paralytica is as yet unknown The several theories are 1) direct action of the spirochetes 2) action of some toxin elaborated by the spirochetes and 3) dis

turbance of the circulation as a result of the action of the spirochetes on the small blood vessels The first theory has not received general acceptance because spirochetes cannot be demonstrated in all cases and because they apparently do not invade nerve cells The second theory is discarded since there is no known toxin elaborated by the spirochetes The third theory while as yet unproved



FIG 5 Spirochetes in the cerebral cortex (Jahnel stain)

seems to be the most acceptable one Occlusion of the cerebral capillaries and venules resulting from the hyperplastic and inflammatory changes in their walls would lead to ischemia and degeneration of the cerebral tissues

Variations in the Pathological Picture — The pathological picture is essentially the same in the various clinical forms of dementia paralytica There are however a few variations which are worthy of note In *juvenile paresis* changes in

the cerebellum and brain stem are more frequent than in the average case Local intensification of the process similar to that seen in Lissauer s paresis is also quite common in juvenile paresis In *senile paresis* there may be foci of softening secondary to arteriosclerosis of the cerebral vessels In treated cases or in the so-called *stationary cases* that is cases with long remission the changes differ from the usual case only in the mild degree of inflammatory reaction and other changes It is thought by some observers that the cases characterized clinically by the occurrence of frequent convulsive seizures *convulsive paresis* are associated with an acute intensification of the typical pathological process This is not however, always true The coincidence of sclerosis of the hippocampal gyrus is common in this type of case but is found also in cases without a history of convulsive seizures

Lissauer and Storch[18] in 1901 described a group of cases which differ clinically from the usual case by the occurrence of focal neurological signs and are characterized pathologically by striking atrophy of the brain, in areas which usually are spared The pathological changes in these cases are not essentially different from that of the usual case All gradations between the average case and the so called Lissauer s type can be found both clinically and pathologically In the typical *Lissauer s paresis* there is the usual atrophy of the frontal lobe and in addition an extraordinary degree of atrophy sometimes unilateral, of the temporal lobe the supramarginal and angular gyri and occasionally of the occipital lobe or paracentral lobule

Microscopically the typical pathological changes are found in the usual sites but in addition some of the atrophic convolutions may show a laminar or pseudolaminar loss of nerve cells with resulting status spongiosus There is a diffuse or focalized loss of myelin in the white matter of the atrophic convolutions The degree of inflammatory reaction in the involved areas is relatively slight and spirochetes are rarely demonstrated

Influence of Treatment on the Pathological Process

Solomon and Taft[19] found regression of infiltrative phenomena toward a less acute form in cases which died after intensive arsphenamine therapy Straussler and Koskinas[20] and others have reported similar changes in cases dying some months or years after malaria therapy In such cases there is a decrease in the degree of inflammatory reaction an apparent cessation of the parenchymatous degeneration and a decrease or absence of spirochetes When death occurred during or shortly after fever therapy there was no apparent change in the pathological process Breutsch[1] believes that the beneficial effect of malarial fever therapy is due to activation of the reticuloendothelial system with an increase in the number and activity of these cells

CLINICAL SYMPTOMATOLOGY

The clinical manifestations of paretic neurosyphilis are protean and may imitate mental disorders of either the organic or functional reaction types The profusion of clinical syndromes by which the disease may manifest itself has led to the paraphrasing of Osler s famous dictum about syphilis to read Know paretic neurosyphilis in all its aspects and you know all of psychiatry The one common denominator of all cases of paretic neurosyphilis is a characteristic cerebrospinal fluid In all untreated cases these characteristic abnormalities the so-called paretic formula afford a simple laboratory method of separating paretic neurosyphilis from all other diseases of the brain Although the characteristic paretic formula may be found in other types of neurosyphilis and is not of itself pathognomonic of dementia paralytica this diagnosis can be excluded when it is not present

TABLE II

SYMPTOMATOLOGY OF DEMENTIA PARALYTICA

Early

1 Irritability or hebetude
2 Excessive fatigability
3 *Forgetfulness*
4 Over suggestibility
5 Personality changes
6 Conduct slump
7 Headaches
8 Change in sleep habits
9 Weight loss

Late

1 Defective judgment
2 Impaired memory
3 Emotional lability depression or elation
4 Lack of insight
5 Confusion and disorientation
6 Poorly systematized delusions
7 Seizures

Dementia paralytica is a chronic disease often requiring many years for its evolution and progress In untreated cases the progress of the disease is progressive and inevitably results in death The duration of the disease varies from a few months to five or occasionally more years The usual life expectancy is two and one half years Spontaneous remissions occur in a small percentage but such remissions usually are only of a few months duration After such a remission the subsequent course of the disease frequently appears to be accelerated

the cerebellum and brain stem are more frequent than in the average case. Focal intensification of the process similar to that seen in Lissauer's paresis is also quite common in juvenile paresis. In *senile paresis* there may be foci of softening secondary to arteriosclerosis of the cerebral vessels. In treated cases or in the so called *stationary cases*, that is, cases with long remission, the changes differ from the usual case only in the mild degree of inflammatory reaction and other changes. It is thought by some observers that the cases characterized clinically by the occurrence of frequent convulsive seizures, *convulsive paresis*, are associated with an acute intensification of the typical pathological process. This is not, however, always true. The coincidence of sclerosis of the hippocampal gyrus is common in this type of case but is found also in cases without a history of convulsive seizures.

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was slurred, and he often used words incorrectly aphasia The right pupil was 4 mm and the left 3 mm in diameter They did not react to light and reacted poorly on convergence The knee jerks and ankle jerks were absent and the Romberg test was positive Position and vibratory sense were impaired in feet and legs

Laboratory data Blood Wassermann reaction was positive Cerebrospinal fluid pressure normal cells 120 per cu mm globulin positive colloidal gold 5554332100 Wassermann reaction positive

Course After six months in the hospital the patient was discharged improved even though he had no treatment He returned six months later in a much worse condition Speech was almost unintelligible and handwriting illegible Memory was faulty Conversation was flighty and incoherent There was marked hypochondriacal preoccupation with body functions He was restless profane confused and easily angered or amused He had many brief seizures which terminated in stupor and death two years after onset of illness

Pathological diagnoses Syphilitic aortitis with incompetence of aortic valve and left ventricular enlargement Syphilitic meningoencephalitis with a) atrophy of frontal temporal and parietal lobes b) internal hydrocephalus c) granular ependymitis and d) degeneration and gliosis of column of Goll and Burdach

A patient may become involved in a variety of difficulties during this period because of poor judgement and uncritical actions which lead to social and legal complications A few cases are illustrative

A school teacher drove to the school supply yard and loaded lumber on his car which he took home intending to build some chicken coops An associate seeing him do this telephoned his wife who easily persuaded him to return the stolen lumber not because he was aware that he was committing theft but because he was easily influenced Only then did the family recalling numerous oddities of behavior over months realize that he needed medical treatment

A factory superintendent found himself restless sleeping poorly having mild headaches unable to concentrate well not enjoying his food and lacking energy As he failed to obtain benefit from psychotherapy and books on how to control his nerves he went to a general hospital where paretic neurosyphilis was diagnosed Based upon his optimistic but unsound judgement that business was going to expand he had caused his firm great loss through huge inventory purchases

Two maiden ladies labored unsuccessfully for more than twenty years to get their dentist brother to forego his Saturday night poker game and beer drinking with his cronies Finally they succeeded but only because the paretic process had reduced his resistance

Occasionally emotionally laden experiences appear to be the precipitants of a paretic psychosis Thus a hotel proprietor became depressed after his hotel

For simplification in presentation the course of the disease in the usual case can be divided into three stages 1) the period of onset, 2) the period of full development of the psychosis and 3) the period of decline and terminal state

The Period of Onset

The period of onset is often called the medico legal period since during this stage before the psychosis is recognized the patient may become involved in legal difficulties The onset of symptoms may be insidious or sudden Often it is only in retrospect after the nature of the disorder is apparent that the slight defects in judgement and minor peculiarities of conduct are appreciated The friends and relatives of the patient then will be able to relate many incidents that take on a new meaning They may recall that the patient had been less aggressive less competent less interested in his affairs and had shown other symptoms of early mental deterioration such as forgetfulness tardiness, discourtesy, carelessness of personal appearance unsound judgement undue suggestibility, irrascibility or self assertiveness Periods of depression with ideas of guilt alternating with periods of elation and undue optimism may have occurred In some patients there may be insomnia nervousness and a host of bodily complaints leading to an erroneous diagnosis of ' neurasthenia These alterations of personality and conduct may be of a minor degree occurring only at intervals and covering a time expanse of many months or they may progress very rapidly The following case, which came under observation in the period before fever therapy was in use illustrates the insidious onset of mental symptoms accompanied by somatic complaints

Tabo Paretic Neurosyphilis of Insidious Onset — History J M was a mill worker aged 49 who was brought to the hospital by his family because of his queer behavior He had been well and working regularly until the onset of his illness He drank moderately being known as a Saturday night drinker' but had been industrious and supported his family despite his alcoholism About 6 months before entry to the hospital he began to have headaches was nervous and slept poorly He became apprehensive over the future of his children and often talked rather incoherently on this topic His employer reprimanded him for being late and neglecting his work On one occasion he arrived for work several hours too soon His conversation became foolish and he could not be entrusted with simple errands Lately he had taken to running away and hiding in bushes along the roadside On one such occasion he had been apprehended by the police There had been a weight loss of about 20 pounds

Examination The patient was rather poorly nourished The teeth were carious and the skin was dirty The heart was enlarged and there was a diastolic murmur over the aortic area There were tremors of the lips and tongue Speech

of his hospital admission showing nothing suggestive of mental disorder As he walked to his place of employment where he was a clerk on a salary of twenty dollars a week he stopped to order two Rolls Royce cars insisting that he was a multimillionaire and had a monopoly on the world s coffee market From that moment he had delusions of grandeur and was excited

Another man on leaving a theater with his wife grabbed a handbag from an unknown woman and ran down the street until apprehended by the police His state was such that the officer had no doubt but that he was in need of hospital care

A patient was brought into the hospital during the night by the police because he had run amuck at his rooming house breaking up the furniture and shouting loudly The next morning he was quiet cooperative and showed no evidence of mental disturbance Not until many days later did another outbreak occur following which there was evidence of mental deterioration

Some patients come to the notice of physicians because of acute alcoholic intoxication or delirium tremens on recovery from which the evidence of paretic neurosyphilis is found Whether the alcoholic debauch precipitated the paretic psychosis or merely masked an already existing psychosis is difficult to decide

The Established State of Dementia Paralytica

Dementia paralytica is primarily and most importantly a psychosis It is the effect of the disease on the intellect behavior and personality of the patient that is of major concern In the past when there was no effective treatment for the disease and death almost inevitably was but a short way off by the time the diagnosis unfolded itself, the mental disability was a grave and pathetic problem Even today one is always faced with the serious question of how much mental impairment will remain after treatment has halted the progress of the disease In the premonitory period all the mental and neurological symptoms do not depend on destruction of nerve cells there is a functional derangement which in part may be reversible Nevertheless in general when clear cut mental deterioration has once occurred it is probable that structural damage is more than minimal in amount

Although the psychotic pictures presented by paresis are multiform reproducing all conceivable psychiatric syndromes it has been customary nevertheless to divide the cases on basis of the most conspicuous clinical symptom

The Expansive Grandiose Type (The So called Classic Form) — Although this type of psychosis occurs in only 10 to 20 per cent of early cases it has become fixed in the minds of many as the classic form of the disease This is probably due in part to the physician s memory of amusing examples presented at clinics and because in the later stage of the disease there is some tendency for many paretics to take on a grandiose coloration After a longer or shorter preliminary

burned down Since the building was not insured and all of the patient's life savings thereby were lost there seemed a reasonable explanation of his depression On the other hand for an experienced hotel man to buy a firetrap hotel and fail to insure it was prima facie evidence of judgement defect which was confirmed by the further study of his case

A young woman on the basis of a negative blood test was told that she had been 'cured' of a syphilitic infection which she had acquired from her husband who had died of neurosyphilis She became very happy and her gayety which at first seemed readily understandable, became somewhat less appreciated by her family when she began to spend beyond her means get drunk frequently and associate with undesirable companions As the exuberance increased hospitalization became necessary The cerebrospinal fluid showed the characteristic paretic formula and gave a more reasonable explanation of her psychotic symptoms than the joy of hearing that she was cured of syphilis

A cerebral accident with monoplegia, hemiplegia aphasia or convulsion or a confused spell may be an early indication of paretic pathology and precede the mental changes by months or even years It is characteristic for the symptoms in such cases to be transient lasting as a rule a matter of hours or at most a day or two Whereas these temporary accidents should make one think always of syphilis of the brain only too frequently when such patients are admitted to a hospital, they are discharged without examination of the cerebrospinal fluid when symptoms improve Later with or without subsequent 'shocks" the paretic syndrome becomes obvious

It is not unusual for a convulsion to be followed immediately by a full blown psychosis An individual who has shown little or no evidence of mental disorder may have an epileptiform seizure and on regaining consciousness show psychotic symptoms A psychosis developing rapidly after an initial convulsion in a middle aged person always is highly suggestive of dementia paralytica Similarly after other episodic cerebral attacks with transient neurological signs such as aphasia or hemiplegia well developed psychotic manifestations may be present Frequently confusion is the outstanding feature of the psychosis, but to this may very shortly be added other distinctive features of organic brain disease Improvement in both the mental and neurological symptoms is common only to be followed by gradual or sudden relapse after another seizure Mental symptoms also may occur suddenly without preceding physical upsets A person apparently in the best of health may suddenly have a brain storm and thereafter show a classic paretic syndrome or the period of psychotic behavior may be of short duration with apparent recovery for days or weeks, until a new episode leads to more enduring symptoms

The following cases illustrate the precipitous onset of psychotic symptoms

The wife and sister of one of our patients insisted that he left home the morning

Mental tests were performed poorly because of inattentiveness and there was impairment of his memory The pupils were slightly irregular and reacted sluggishly to light but well to convergence His speech was dysarthric and the handwriting was tremulous There were perioral and lingual tremors The tendon reflexes were lively but plantar reflexes were normal

Laboratory data Blood Wassermann reaction was positive Cerebrospinal fluid 84 lymphocytes total protein 96 mgm per 100 c c colloidal gold 5554332100 Wassermann reaction strongly positive

Course The patient was given 10 malarial chills and then alternating courses of tryparsamide and bismuth He improved considerably being able to resume his former occupation The cerebrospinal fluid became negative after $2\frac{1}{2}$ years of treatment His earning capacity is not as great as before his illness but in general the treatment result was excellent

The Manic Type — Many patients show mental symptoms that are hardly distinguishable from those seen in the manic state of manic-depressive psychosis Over activity with physical restlessness lack of sleep distractability punning over talkativeness and playfulness are outstanding Before the evidence of mental deterioration becomes evident there is little in the symptomatology that will enable one to recognize the underlying paretic process This latter possibility must be excluded always in any case of manic-depressive psychosis It is frequently stated that the patients with the manic type of dementia paralytica lack the joyful zestful evidences of the true manic or that the humor is not as real nor the wit as lively In an individual case however such factors are most difficult to evaluate The following case history illustrates the occurrence of manic symptomatology in a patient with dementia paralytica

History The patient a 58 year old architect entered the hospital because of restlessness and excitability Three days before he left home in the morning and went to his office During the day he became excited over the prospect of a new contract which his company had just signed He neglected to eat his lunch and was unable to settle down to his work that afternoon That evening he went to several night clubs and shows This excessive activity continued for several weeks until his admission to the hospital which was precipitated by an altercation with a shopkeeper Only then did his family realize that his behavior had been abnormal He had had gonorrhoea and syphilis when he was 28 years old and received sporadic antisyphilitic treatment for one year His wife had been pregnant only once and that pregnancy ended in a miscarriage

Examination The patient was restless and hyperactive insisting on pacing around the room during the examination He was distractible Memory fo recent events was faulty as his judgement was impaired He had no insight into his illness His speech was dysarthric Pupils were unequal and irregular but reacted to light and on convergence The tendon reflexes were hyperactive

period the patient enters a state in which the boundaries between reality and imagination are no longer clear, critical judgement diminishes to the vanishing point, and the world apparently is conquered The expressions of grandeur take many forms probably directed, in part at least by the patient's prepsychotic desires and ambitions Thus one patient considers himself the richest man in the world the owner of diamond studded airplanes Another brags of his great strength and fine physique A third boasts of the beauty of his singing voice, while another proclaims himself emperor of the world More moderate claims are made by patients which if the examiner is not well advised may seem factual The exaggerated claims rarely appear incongruous to the patient even though all outward evidence belies them

With the grandiosity usually goes euphoria an abnormal sense of well being The patient will tell how fine he feels a significant expresson often heard that gives the initiated cause for concern is I never felt so well before in all my life Suggestibility usually is marked, with little tact and cajoling the patient can be persuaded to do almost anything that is asked of him In this state the higher intellectual functions usually are badly impaired

The Simple Deteriorating Type — The essence of dementia paralytica is mental deterioration This is characterized by memory defect impairment of judgement excessive lability of mood and loss of the fine qualities that make up the personality of an individual It is the loss of these that stands out prominently in the simple dementing type of dementia paralytica As the memory becomes more clouded the judgement of the individual more defective and the emotional stage more labile, one has the characteristic picture of "dementia This dissolution of intellectual faculties proceeds to a state comparable to imbecility or idiocy The following case history illustrates the simple dementing form of the disease

History The patient a 46 year old insurance agent, who had been successful in business and had enjoyed good health was brought to the out patient department by his wife because he had lost his position During the past several months perhaps the past year he had become careless about his appearance and failed to keep appointments with prospective clients On one occasion he sold a large policy but neglected to fill out appropriate forms He had been careless in accounting to his company for certain collections of premiums which he customarily made About 2 weeks before this time he had been reprimanded by the manager of the local branch office and had resigned Since then he sat around his home taking no interest in the affairs of his family There was no history of syphilis

Examination The patient appeared dazed He had entered the hospital without removing his hat and his vest was soiled with food which he had had that morning for breakfast The patient declared that there was nothing wrong with him except that he was "run down from overwork' His mood was normal

The Paranoid Type — Occasionally the paretic patient presents a symptomatic picture that is similar or identical to that which one sees in certain psychoses classified as paranoid The mental symptoms are characterized by well systematized delusions with good retention of most of the intellectual faculties Were it not for the neurological signs and the laboratory findings one would judge the patient to be suffering from paranoia *The results of treatment in these cases* are interesting in that although the spinal fluid may become normal and tremors and speech defect greatly improved the patient continues to hold to his paranoid delusions Indeed one is led to speculate as to whether one is not dealing fundamentally with two separate conditions namely a more or less asymptomatic neurosyphilis and a paranoid psychosis *In the few cases of this category that* we have seen the course of events however is somewhat different from that ordinarily seen in the well established paranoid psychosis in that after the lapse of one two or three years the symptoms ameliorate the delusions become less pressing and after a long period during which ultimate recovery seems remote psychological adjustment gradually improves so that the patient is able finally to return to useful life

Paretic Neurosyphilis Paranoid Type —The patient was a 35 year old lithographer who was committed to the hospital by court order In the preceding months his business had fallen off he had become careless in his dress and had beaten his wife on several occasions He was brought to court by his wife and after commitment to the hospital he refused to talk except in a whisper explaining that his enemies might overhear his conversation He thought the samples of his blood for serological tests were being sent to the Federal Bureau of Investigation for special tests He complained that experiments were being performed on his body at night while he was asleep The neurological examination was essentially negative The blood serology was positive and the cerebrospinal fluid showed the characteristic paretic formula He was treated with malaria fever followed by chemotherapy without any change in his delusional ideas One year later aided by his brother he escaped from the hospital and moved to a western city where he obtained employment as a linotype operator He was quite successful in this job but when examined by one of us on a visit to the east paranoid delusions still were present He presented a long and involved explanation of how ordinary news items were really messages being sent to him in code

Not all cases fit into these neat compartments There are many other varieties of paretic mental abnormalities but the main point is that in the well established phase of the disease the patient obviously is suffering from a psychosis which is induced by the destruction of cerebral cortex but whose form is determined in part by the nature of the patient s personality

Laboratory data The blood Wassermann test was positive Cerebrospinal fluid 1 0 cells globulin positive total protein 78 mgm per 100 c c, colloidal gold 5555432100 Wassermann reactions strongly positive

Course Patient was treated with malaria followed by tryparsamide and bismuth He improved but was unable to continue work as an architect When last seen his mood was normal, memory quite good tremors had disappeared and cerebrospinal fluid was almost normal

The Depressed Agitated Type — The patients falling into this group are from the clinical standpoint very similar to those with depressed or agitated states of other etiology such as manic depressive psychosis and involutional melancholia Sadness and unhappiness self accusations and recriminations often with marked delusional trends are seen The patient may appear agitated and fearful may believe that he has committed a grievous sin perhaps an unpardonable sin, or may talk of being infected with a horrible disease which he is spreading through out the community Still others talk about bodily diseases in curious terms stating for example that their blood has all turned to water that they have neither stomach nor intestines that their heart has stopped beating and that their muscles have turned to stone The depressive form is illustrated in the following case history

History The patient was an Italian aged 52 employed as a barber About 6 months ago he began to complain of nervousness insomnia and indigestion His local physician prescribed phenobarbital which gave little or no relief In the next few months he became depressed entertained ideas of unworthiness and had thoughts of suicide He was sent to a small hospital for treatment of a nervous breakdown After 3 months he improved somewhat and was discharged He came to the out patient department of the Boston City Hospital with the same complaints There was no history of syphilis

Examination The patient was obviously depressed He moved slowly and took no interest in the examination He was oriented for time but not for place and lacked insight into his condition He refused to cooperate for parts of the examination The pupils were small irregular and reacted imperfectly to both light and convergence There were tremors of outstretched fingers tongue and lips Tendon reflexes were hyperactive

Laboratory data The blood Wassermann test was positive Cerebrospinal fluid 30 lymphocytes globulin positive total protein 110 mgm per 100 c c, colloidal gold 5544321000, Wassermann reaction strongly positive

Course The patient was inoculated with tertian malaria which did not take and he was sent to the Boston Psychopathic Hospital for artificial hyperthermia treatment After a series of fever treatments in the fever cabinet there was gradual remission of his symptoms and he was able to return satisfactorily to his work as a barber

vented death results either from convulsive seizures or from what is apparently a paralysis of respiration

Nothing can be more distressing than the state of patients in this type of disorder It should be emphasized again that under modern methods of treatment it is extremely rare for a patient to reach this stage

Neurological Signs

The most characteristic and important neurological signs in dementia paralytica are pupillary abnormalities paralytic facies tremors speech and handwriting disorders and change in the tendon reflexes

It should be pointed out that the neurological abnormalities are not essential for the diagnosis In the earlier phases of the disease no physical signs may be discovered and even the most thorough neurological examination may give no clue to the underlying process This fact should be born in mind always otherwise grievous failures in diagnosis will result There is probably no experienced psychiatrist who has not committed errors in diagnosis by relying too much on the presence or absence of neurological signs to establish or exclude the diagnosis

A second point of importance is that signs pointing to permanent focal nervous system lesions are not to be considered part of the paretic process Abnormal neurological signs may appear after seizures but usually are transitory Persistent focal signs indicate either another diagnosis or else a complicating lesion of the true paretic pathology

TABLE III

Neurological Signs of Dementia Paralytica

Common

- Pupillary abnormalities
- Dysarthria
- Relaxed expressionless facies
- Tremors of facial lingual and hand muscles
- Impairment of handwriting
- Abnormality of tendon reflexes
  - (a) Hyperactive
  - (b) Absent

Rare

- Focal neurological signs — hemiparesis hemianopia etc
- Eye muscle palsies
- Optic atrophy
- Pathological reflexes
  - (a) Inequality of tendon reflexes
  - (b) Babinski sign

Period of Decline and Terminal State

As the psychosis continues little by little the mental and physical deterioration becomes more conspicuous Grandiosity, mania depression agitation or paranoid ideas recede to the background The patient becomes less active his interests diminish and whatever the original symptomatology may have been, dementia becomes the outstanding characteristic This period of the disease lasts for a varying period of time in some it is a matter of a few weeks in others a matter of two to three years

As a rule seizures occur during this period of the disease following which there is likely to be not only paralytic phenomena but even more strikingly a considerable increase in the dementia The seizures may be either apoplectiform or epileptiform in type the latter varying in frequency and severity At times patients will pass into a status epilepticus lasting for hours or a day or two The apoplectiform attacks may be generalized or unilateral and are characterized by the fact that they leave the patient with evidences of paralysis Frequently the patient will have a convulsion following which there will be a very complete and characteristic hemiplegia with exaggerated reflexes, positive Babinski sign and ankle clonus on the affected side Such paralyses in a paretic are characterized by their relatively fleeting character Often at the end of twelve seventy two or ninety six hours the paralysis will disappear and the abnormal reflexes no longer will be found but occasionally there may be some residual motor deficit After a variable period of time with or without convulsive episodes the patient reaches what may be termed the terminal state of the disease

There is no clear cut demarcation between the so called established state of the disease and the terminal period Once the patient becomes bedridden, generally he has reached the terminal stage As the disease progresses the motor centers and corticospinal tracts are destroyed with resulting paralytic phenomena As the patient loses voluntary power he becomes confined to bed This paresis is generalized and progressive Because of this feature the term, general paralysis of the insane came into use in a description of the disorder

The loss of voluntary motor power also affects the bladder and rectal sphincters Nursing care at this period becomes extremely difficult With emaciation inability of the patient to move about tendency to soil himself and with lessened viability of the skin bedsores are almost inevitable The general state of the patient is so poor than an intercurrent infection such as pneumonia cystitis and ascending pyelitis or generalized septicemia from infected bedsores are among the usual causes of death

The duration of life in this terminal stage of the disease varies from a short period to many months being in part dependent upon the adequacy of nursing care which the patient receives If these intercurrent infections can be pre

of the disease In the section on pathology it is shown that either the posterior or lateral tracts of the spinal cord or both may have degenerated in paretic neurosyphilis hence the variation in the activity of the reflexes It is only very late in the disease or under very unusual circumstances that there is enough destruction of the corticospinal tract for abnormal plantar responses or ankle clonus to appear

Congenital Paresis

The clinical symptomatology in congenital paretic neurosyphilis varies in only minor details from adult neurosyphilis The most striking differences are a) the frequent association of feeblemindedness in the congenital cases b) variations determined by the occurrence of syphilitic encephalitis in an immature stage of physical mental and personality structure of the individual and c) the resistiveness of the congenital form to therapy

Senile Paresis

Here the clinical picture is complicated by the changes of senility There may be symptoms resulting from diffuse or focal damage to the brain by cerebral arteriosclerosis Thus persistent hemiplegias and other focal neurological signs are commonly seen in these cases

Lissauer's Paresis

As mentioned before the usual case of paretic neurosyphilis shows at autopsy diffuse atrophy of the cerebral cortex which is most intense in the frontal lobe and progressively decreases in intensity toward the posterior poles of the hemispheres Such a distribution of atrophy is rather to be expected from the character of the clinical course which offers no symptoms and signs of a focal nature In contrast to these usual cases are those which during life show focal signs and at autopsy striking atrophy of certain convolutions of the brain not usually affected The first thorough studies of these atypical cases of paretic neurosyphilis were made by Lissauer and Storch[15] and by Alzheimer[7] who suggested that these cases be called Lissauer's dementia paralytica

Cerebrospinal Fluid

The cerebrospinal fluid abnormalities which are present in patients with dementia paralytica are so constant and characteristic of the disease that they are known as the paretic formula While these abnormalities are not pathognomonic of dementia paralytica since they may be found in any type of neurosyphilis they are present in 100 per cent of the untreated cases of dementia

Pupillary disorders may be found in all forms of neurosyphilis and are not diagnostic of any one type These pupillary changes include irregularities in outline, inequality in size and impairment of light and accommodation reflexes The true Argyll Robertson pupil is not encountered often early in the course of the disease Instead the pupils often are large rather than myotic and may be fixed to both light and convergence In many cases the pupils change in the course of a few months from normal to Argyll Robertson type to completely fixed pupils

As the paretic process progresses and the motor nerve cells of the cerebral cortex disappear, there is an advancing infirmity of the body manifested by slouching carriage hypotonia and flattening and smoothing out of the facial lines This latter often is called the "paralytic" facies and may enable an experienced physician to recognize a paretic at a glance

Tremors of the facial muscles of the extended tongue and of the outstretched fingers sometimes occur very early An attempt on the part of the patient to pronounce difficult phrases serves to make tremors apparent about the eyes and at the corners of the mouth and in the lips The tremors of tongue and fingers usually are coarse in variety and may be gross enough to interfere with coordinated movements such as writing and clear enunciation They generally cease when muscles are in complete repose

The disorder of speech probably is the most characteristic sign of paretic neurosyphilis To the ear accustomed to hearing the speech of the paretic it is possible in many instances to be sure of the diagnosis after hearing but a few words spoken Loss of clarity of enunciation is likely to be the first defect the patient slurring consonants especially when excited or talking rapidly Later the articulation becomes less and less precise Not only is thickness of speech and tremor of the voice evident but letters and syllables are elided words are mispronounced and the voice breaks In some instances these speech disorders are best perceived in spontaneous talk in other instances requiring the patient to repeat test phrases will bring out the defect Among such phrases the following may be mentioned "Methodist Episcopal" suicidal electricity, hippopotamus, hippopotamus "Boston Psychopathic Hospital", "around the rugged rock the ragged rascal ran To these dysarthric difficulties are often added aphasic disturbances which range from an occasional inability to name objects to a complete or global aphasia

Like his speech, the paretic's handwriting may be very suggestive of the diagnosis giving a clue to intellectual slipping as well as motor disturbance One notes not only tremor as shown by waviness of the lines and incoordination due to uneven pressure of pen on paper but also poor judgement as to proper spacing of words misspelling transposition and omission of letters

Tendon reflexes may be normal increased, decreased or absent at any stage

demented patient is also very strong evidence against the paretic type of involvement Further the reaction to antisyphilitic treatment is helpful If it is impossible to decide whether the patient has paretic or meningovascular syphilis the wise course of action is to give fever therapy

Cerebral Arteriosclerosis — The mental symptoms of cerebral arteriosclerosis are often indistinguishable from those of paresis The presence of arteriosclerosis in the retinal and peripheral vessels as well as the absence of the characteristic changes in the cerebrospinal fluid should lead to the correct diagnosis

Manic Depressive Psychosis — As previously mentioned the onset of dementia paralytica may be manifested by symptoms similar to those seen in patients with manic depressive psychoses The presence of pupillary abnormalities and of other evidence of organic disease of the central nervous system should lead to the suspicion of the diagnosis of paretic neurosyphilis The finding of mental deterioration on psychometric testing and the results of examination of the cerebrospinal fluid will establish the diagnosis

Schizophrenic Psychosis (Dementia Praecox) — Schizophrenic symptoms are uncommon but paranoid formulations and oddities of conduct and thought of a schizophrenic nature occur in a small number of cases of paresis in the early stages Hallucinations are seldom seen except after fever therapy The differential diagnosis is made from the results of the neurological examination and study of the cerebrospinal fluid

Psychoneurosis — Neurasthenic symptoms frequently are present in the early stages of dementia paralytica Similarly the fleeting paralysis of early paresis may be mistaken for hysterical manifestations Therefore one must be careful to exclude paresis in patients with neurasthenic and hysterical symptomatology by careful neurological and serological examination

Alcoholic Psychoses — Delirium tremens and the acute alcoholic hallucinoses are not likely to offer much difficulty in differential diagnosis Nevertheless the excessive use of alcohol is a frequent symptom of paretic neurosyphilis and the mental deterioration which is present in chronic alcoholics may be confused easily with that of dementia paralytica On the physical side pupillary abnormalities tremors and hyperactive reflexes are common to both conditions In many cases the differential diagnosis can be made only by the results of the examination of the cerebrospinal fluid

Various Organic Diseases of the Brain — The symptomatology of dementia paralytica may be simulated by a wide variety of organic diseases of the brain such as cerebral tumor cerebral abscess multiple sclerosis pernicious anemia senile dementia Pick s disease Alzheimer s disease and Huntington s chorea The typical symptoms of these disorders as well as the normal serological tests are sufficient to establish the correct diagnosis It must be remembered however that any of these conditions may occur in a patient with abnormalities in the

paralytica, and the latter diagnosis is not tenable unless they are present The characteristic abnormalities of the paretic formula are 1) increase in cells ranging from 10 to 100 consisting chiefly of lymphocytes to which are added a few plasma cells and macrophages 2) increase in the total protein content with values commonly in the range of 45 to 100 mgm per 100 c c Usually there is a disproportionate increase in the globulin fraction with resultant positive globulin tests (Pandy and Ross Jones) 3) a strongly abnormal colloidal gold reaction, which is practically always of the first zone type (5555544321) but occasionally of the midzone type (11 3443211) and 4) strongly positive Wassermann or precipitin tests for syphilis

These changes in the cerebrospinal fluid are quite resistant to treatment with the usual antisyphilitic remedies, and they respond very slowly to fever therapy with usually several to many years between the fever therapy and reversal of the fluid to normal

Differential Diagnosis

In the differential diagnosis it is obvious that one has to consider almost all forms of mental disorder With the exception of meningovascular neurosyphilis the differential diagnosis between dementia paralytica and other diseases of the nervous system which are accompanied by mental symptoms can be made without great difficulty by the results of careful neurological and psychiatric examination and by examination of the cerebrospinal fluid The characteristic cerebrospinal fluid abnormalities establish the diagnosis of dementia paralytica in a patient with signs and symptoms of cerebral involvement except in the rare instances where there is a coincidence of asymptomatic neurosyphilis and some non syphilitic cerebral disorder

Meningovascular Neurosyphilis — It is often difficult if not impossible to distinguish between the paretic and meningovascular so called cerebral syphilis forms of neurosyphilis It is important to decide whether the pathology in a given case is essentially meningoencephalitis or vascular because the initial treatment of these two conditions is different Signs of focal involvement always suggest the probability of the meningovascular rather than the paretic form Extra ocular palsies monoplegias paraplegias or hemiplegias aphasia optic atrophy nerve deafness and the like usually indicate a vascular or meningeal form of the disease It must be borne in mind that with meningovascular neurosyphilis there may be mild or marked mental symptoms Further that a combination of meningovascular neurosyphilis with the paretic form may occur in any given case If the symptoms make their appearance in less than three or four years after the primary infection it is highly probable that they are not due to paretic neurosyphilis A weak cerebrospinal fluid formula in an untreated

There is good evidence to show that if malaria is not followed by chemotherapy relapses will occur in approximately 25 per cent of cases If the patient does not respond adequately to the first course of fever and chemotherapy a second course of fever occasionally will prove beneficial

There is no parallelism between the improvement in the cerebrospinal fluid and the remission of symptoms nor does the spinal fluid give complete evidence of success or failure Many patients in whom the cerebrospinal fluid remains strongly positive for years maintain perfectly good mental and physical status and of course other patients in whom the cerebrospinal fluid becomes less abnormal or negative have suffered such extensive damage to the nervous system that the clinical results are entirely unsatisfactory If following fever the cerebrospinal fluid shows a tendency to become more strongly abnormal further fever treatment is indicated Of the cerebrospinal fluid abnormalities the most valuable guide in the predicting of relapse is the cell count An increase in the number of white cells in the spinal fluid is evidence of activity and strongly suggests an impending relapse

In debilitated patients it is often wise to give tryparsamide for several weeks until their physical condition has improved sufficiently to tolerate malarial fever Some fever cabinet bouts may be given during this period with benefit both to the general physical health of the patient and to the paretic process In patients with hypertension pulmonary cardiac or renal disease fever cabinet is the method of election because of the risk of using malarial method

There are a number of methods by which fever may be safely produced for therapeutic purposes They are

1 Injection of foreign protein
2 Injection of pyrexial drugs
3 Mechanical fever producing devices
4 Induction of febrile diseases

Foreign Protein Methods of Fever Therapy — The most satisfactory of these methods and the one that has been used most extensively is the intravenous injection of typhoid and paratyphoid vaccines The usual practice is to inject 50 000 000 dead organisms of the standard typhoid paratyphoid vaccine intravenously Within 30 to 90 minutes the patient has a chill and the body temperature rises to 101 to 106 F and remains elevated for from two to several hours Since the standard preparation of vaccine contains 2 500 000 000 organisms per c c the required number of organisms can be obtained by the dilution of 1 c c of vaccine with 99 c c of normal saline (dilution of 1 to 100) so that each cubic centimeter of the mixture contains 25 000 000 organisms The amount of each succeeding injection must be increased usually doubled in order to obtain an adequate febrile reaction It is often difficult to obtain a satisfactory

cerebrospinal fluid as the result of the coincidence of asymptomatic neurosyphilis This is particularly true of patients with symptoms of increased intracranial pressure and focal neurological signs which are rarely found in paretic neurosyphilis and are due more commonly to an expanding intracranial lesion

TREATMENT

In all cases of dementia paralytica fever therapy is the treatment of choice In our opinion malaria is the most effective fever method and should be induced at the earliest possible moment after the diagnosis has been established The relative merits of malaria and mechanically produced fever have long been the subject of lively argument Among experienced workers in the field there are advocates of both methods Detailed statistical analyses have offered little assistance in deciding this matter because no two groups of cases treated by different methods are strictly comparable Neymann[22] in discussing the comparative value of artifical fever and malaria quotes Kraepelin as having analyzed 3 000 cases treated by malaria with improvement in 43 per cent whereas with mechanically induced fever he was able to obtain improvement in 63 per cent of his cases Kuhns[23] in a comprehensive study of the various types of fever therapy reported slightly better results when the fever was produced by the electric blanket or by diathermy than with malaria fever These results as well as those of the Clinical Cooperative Group and others indicate that artificially produced fever is superior to malarial fever The selection of case material and other factors make such a conclusion of doubtful validity, and we believe that in the hands of the average practitioner malarial fever is the safest and most practical method of treating this disease

Chemotherapy —The recommended malarial fever treatment consists of 10 to 12 paroxysms This should be followed by chemotherapy as soon as the patient has regained his strength It is desirable to give approximately a dozen injections of mapharsen or neoarsphenamine for general tonic effect and for treatment of syphilis outside the nervous system Tryparsamide should then be given at weekly intervals for approximately two years If tryparsamide is contraindicated on account of the presence of optic atrophy a trivalent arsenical should be substituted There are as yet no reliable data as to the optimum amount of chemotherapy that should be given The ideal is to continue treatment until the cerebrospinal fluid becomes normal but this may take several years, since only about 10 per cent of cases are reversed in each successive year after malaria e g at the end of 5 years about 50 per cent of cases have normal cerebrospinal fluid Two years is perhaps the optimum length of time for the continuation of chemotherapy except in the few cases in which the cerebrospinal fluid becomes normal at an earlier period

the hot bath first tried by Schamberg and Tseng This method was quite efficient but was abandoned because of the tendency to cause collapse of the patient In order to control the temperature a specially constructed tub with an automatic mixing valve is essential

A modification of the hot bath method is a cabinet in which a hot humid atmosphere is maintained Thus evaporation from the body surface is impeded but not entirely prevented Several machines of this kind have been constructed with similar principles The patient s body is enclosed in a large box from which only the head protrudes A heating element and a humidifier are enclosed The degree of temperature and the humidity both may be controlled mechanically With this type of cabinet a body temperature of 106° F can be obtained in a period of 1½ to 2 hours and can be maintained for any desired period

Another method which utilizes the same principle of creating a hot humid environment is the electric blanket The patient is placed in a sack made of an exceptionally large electric heating pad Like the hot bath this method caused so many unpleasant reactions that it has not been used extensively

Four different methods have been used to produce internal heating namely radiothermy diathermy inductothermy and luminous or radiant heat In radiothermy the individual is placed within a field of short wave radio waves which are concentrated between two condenser plates The heating consists of two 500 watt radiotrons operating at a frequency of from 10 000 to 14 000 kilocycles As these radio waves pass through the body internal heat is developed A temperature of 104 to 106 F can be attained in one hour This method though highly efficient has been discontinued because of the expense of the apparatus the technical problems which arise and the danger of surface burns The diathermy apparatus generates internal heat by electrical waves of 500 to 1 500 kilocycles The electrodes are placed against the patient s body and extremities and the diathermy current is passed through them This method has been discarded also for similar reasons The inductothermy method is based upon the principle of the production of an electromagnetic field in which the patient s body is the core of a secondary coil Luminous heating such as is produced by an ordinary tungsten light penetrates the skin and heats the body tissues and the air about the subject

In order to increase the efficiency of all these methods of internal heating it is necessary to prevent evaporation from the body surface This is done by surrounding the body with warm moist air Therefore all the methods of internal heating usually are combined with external heating In our clinic we use at the present time fever boxes with radiant or luminous heat and humidifier in conjunction with an inductotherm

No one of these methods of mechanical hyperthermia has proved superior to others None of these machines are fool proof their efficiency and safety of

series of febrile bout by this method even though enormous numbers of organisms are injected. It has been shown (Nelson[6]) that this difficulty can be overcome by giving the vaccine in divided doses. With this method the first two or three febrile bouts are produced by a single injection of the vaccine. The subsequent febrile bouts are produced by injecting a small number of organisms followed by the injection of an equal or slightly greater number at the height of the febrile response to the first injection. This method is considered by some as dangerous but with proper care a satisfactory number of febrile responses can be obtained without serious risk. It is good practice to withhold food from the patient for 3 or 4 hours before the inoculation in order to prevent vomiting. Codeine in doses of 3 mgm may be given for malaise. It is best to inject the vaccine on alternate days so that the patient will not become unnecessarily exhausted. Unless the temperature consistently rises above 103° F the fever is not to be considered adequate. The usual course consists of 10 to 12 febrile bouts and may be combined with arsenicals. We have found intravenous typhoid inoculations of value in the treatment of paretic neurosyphilis. It is not as effective as malaria fever but can be used in cases where because of other medical disease malaria cannot be tolerated. It can be used to provoke the first chill after malaria inoculation. In decrepit persons or in cases where the malarial fever terminates spontaneously typhoid vaccine injections can be used to complete the desired number of febrile paroxysms. This method may be substituted in those who are immune to malaria.

There are several other non specific proteins which when given parenterally are effective pyrogens. Among these are boiled milk which is injected intramuscularly in doses of 10 c c. This will induce a febrile response in children but adequate levels of fever rarely are obtained in adults. Another disadvantage is that considerable pain and tenderness and at times even abscess formation occur at the site of the injection.

Injection of Pyrexial Drugs — Several different chemicals have the property of raising the body temperature especially when given parenterally. One of the first drugs used for this purpose was sodium nucleinate. Another is a sulfur preparation sold commercially under the trade name pyrifer. This latter drug is a good pyretic but it is difficult to control the fever thus produced and there is considerable pain and sometimes abscess formation at the site of the injection. So far this and other chemicals have had only a limited use in the treatment of neurosyphilis because the results are in general inferior to those obtained by malaria and mechanical hyperpyrexia.

Mechanical Methods of Fever Production — Increase of heat production or diminution of heat loss tend to raise the body temperature. Each of these processes has been utilized in the mechanical production of fever. The simplest device for raising environmental temperature and preventing heat dissipation is

2 Intravenous inoculation of 3 to 5 c c of malarial blood direct from donor (or citrated blood)
3 Take temperature pulse and respiratory rate every 4 hours until first chill every hour or every one half hour during rise of fever and every 2 to 4 hours in interval between chills
4 Tepid sponge for fever over 106 5 degrees
5 Blood pressure determinations twice daily — once during height of fever
6 Give ephedrine sulphate ⅜ grains twice daily for systolic pressure less than 100 mm of mercury
7 Examine urine every 2–3 days after fever starts
8 Hemoglobin and red count every 3 to 4 days after first chill
9 Blood non protein nitrogen every 5 days
10 Palpate abdomen for spleen daily
11 Force fluids milk cream orange juice etc Encourage patient to eat in intervals between the fevers
12 After desired number of febrile bouts stop fever by giving quinine 0 3 gram t i d for 7 days or atabrine 100 mgms t i d for 10 days
13 High caloric high vitamin diet after cessation of fever
14 Iron for anemia

The most practical technique of inoculation is the intravenous injection of blood withdrawn from an infected patient It is possible to transmit malaria by allowing infected mosquitoes to bite the patient or by injection of ground up suspension of salivary glands of infected mosquitoes but these methods entail the keeping of mosquitoes and the cure of the infection is more difficult Three to 5 c c of blood can be transferred from one patient to another without the use of any anticoagulant or preservative If however the malaria blood must be sent from a distance 1 c c of 2½ per cent sodium citrate should be added to each 10 c c of blood The plasmodia in citrated blood will remain virulent from 12 to 24 hours and the addition of 1 c c of 5 per cent glucose will preserve them for as long as 36 hours Potent inoculable material thereby may be shipped long distances by air mail It makes no difference at which phase of the malarial paroxysm the blood is withdrawn Matching of the blood is not necessary in the small amount used and there is no danger of transferring spirochetes from a paretic patient Intravenous intramuscular or subcutaneous routes may be employed The shortest incubation period 3 to 5 days will follow the intravenous injection the longest 15 to 30 days follows subcutaneous injection The incubation period depends to some extent on the size of the original inoculum

Not all patients are equally susceptible to vivax malaria Colored patients from the southern states and individuals who have resided in Mediterranean countries almost always are immune If the patient has been previously inoculated with tertian malaria he is apt to be resistant to re inoculation unless it is performed within a few weeks Quartan malaria can be substituted in these cases One of the important advantages of direct transmission of malaria from patient to patient is that by eliminating the natural vector of the disease the sexual forms of the parasite gametocytes gradually disappear Thus a very

performance depend on the skill and experience of the operator An experienced attendant must be constantly present throughout and following the period of hyperthermy A physician must be in constant attendance also Unless these conditions are possible such treatment should never be attempted The dangers of these methods are burns fatal hyperthermia and medical shock from exhaustion and depletion of body fluids When properly controlled, the mortality rate is lower than that of malaria therapy

The proper care of the patient in the mechanical hypertherm is so complicated that no attempt will be made to discuss the technical details It is our experience as well as that of others that malaria is better than artificially produced fever even when the same number of hours of fever is given

The standard method at the moment for the treatment of paretic neurosyphilis by the fever cabinet is a course of 10 to 12 fever treatments in each of which a temperature of 105 to 106° F is maintained for 3 to 5 hours The treatments are given once or twice a week Artificial hyperthermia can be given to some patients who are unable to tolerate malaria Chemotherapy can be given to patients at the height of the febrile responses It is postulated that the drug enters the nervous system more rapidly and in greater quantities at such a time

Induction of Febrile Diseases — The simplest and most effective febrile disease for the treatment of paretic neurosyphilis is benign tertian malaria The contra indications for the use of malaria are 1) severe debilitating disease of any kind 2) pulmonary tuberculosis 3) marked hypertension 4) cardiac decompensation and 5) chronic Bright s disease

Before submitting a patient to malaria a careful physical examination should be made to determine the existence of any of these complications Plasmodium malariae the parasite of quartan malaria can be substituted in patients who are immune to the benign tertian form The disadvantages of the quartan type are the long incubation period of two to six weeks the interval of several days between chills rather low fevers and greater difficulty in curing the infection Plasmodium falciparum the parasite of aestivo-autumnal type of malaria, is highly malignant and should not be used for therapeutic fever Deaths have occurred from the accidental inoculation of patients with this type of malaria For this reason the blood of patients who have lived in the tropics should not be used in the inocula tion of other patients There seems to be no fundamental difference in the therapeutic efficacy of benign tertian and quartan malaria

TABLE IV

ROUTINE FOR MALARIA THERAPY

1 Careful examination of patient with especial attention to cardiovascular renal and pul monary systems including examination of urine determination of serum non protein nitro gen blood hemoglobin and red cell count and x ray of lungs and heart

and gastric crises in tabetics and psychotic symptoms in paretics often are exacerbated by the fever and must be controlled by analgesic and sedative drugs respectively. The blood pressure should be measured twice daily. Usually there is some fall in blood pressure during the paroxysms of fever. If the systolic pressure declines below 100 mm of mercury pressor drugs may be given. We prefer ephedrine sulphate 22 mgm twice daily. If this does not control the hypotension and the blood pressure continues below 70 the malaria should be terminated. A sustained pulse rate of over 120 during normal temperature or above 150 during the height of fever and auricular fibrillation are also indications for interrupting the fever. Estimation of hemoglobin and counts of red blood corpuscles should be made every 3 to 4 days. The urine should be examined every two to three days and serum non protein nitrogen determined every five days. If the hemoglobin falls below 50 per cent, if the non protein nitrogen rises above 80 mgm per 100 c c or if intractable vomiting, hematuria, severe jaundice, edema or pulmonary disease occur the malaria should be terminated. Since there is a loss of chlorides through excessive perspiration it is well to administer 5 to 6 grams of sodium chloride daily in the form of enteric coated pills.

The malaria may be terminated by giving quinine sulphate 0 3 gm three times daily for 7 days. Usually one chill can be expected after the institution of quinine therapy. The quinine can be administered intravenously in the form of the dihydrochloride or hydrobromide salt in doses of 0 5 mgm, 5 c c of a 10 per cent solution, in the case of intractable vomiting or when it is necessary to terminate the infection immediately. The drug should be injected slowly. Atabrin in dose of 100 mgm three times a day may be substituted for quinine. Neoarsphenamine is also a good plasmocidal drug. In the small percentage of patients in whom the malarial fever terminates spontaneously injections of typhoid vaccine may be used to finish out the course. We have found this combination of malaria and typhoid useful in debilitated patients and those suffering from some complicating medical disease.

After the course of malaria the patients are apt to be quite weak and exhausted. It is desirable to give a high vitamin high caloric diet and ferrous chloride 0 3 gm three times a day if there is anemia. A fairly prolonged hypotension may follow malaria. This can be controlled by ephedrine sulphate or benzedrine. The patient should remain in bed for several days after the last bout of fever.

There is always some risk in exposing a patient to malarial therapy. The actual mortality rate has varied in different clinics from less than one per cent to as high as twenty per cent, depending probably upon the degree of selection of cases and on the care given to the patient during the fever. In clinics where malaria has been used a great deal the mortality rate usually is under four per cent.

Penicillin Therapy. — Very little can be said at the present time regarding the value of penicillin in the treatment of dementia paralytica. Too few cases

benign form of malaria is produced Often the infection will terminate spontaneously or a single dose of either neoarsphenamine or quinine will end the infection

The course of tertian malaria varies considerably from case to case During the incubation period the patient may be ambulatory or may return to work After the incubation period of 3 to 5 days a low grade fever of 100 to 102° F appears and remains for 24 to 48 hours or until the first sharp rise in temperature The first few paroxysms of fever may be irregular and the temperature may remain above 103° F for 48 to 7 hours but within 3 or 4 days the regular pattern of tertian chills on alternate days establishes itself In some cases the febrile bouts gradually become daily probably because a double tertian infection has been contracted The typical paroxysm of fever is preceded by a chill, malaise and nausea and is followed by a rise of temperature to 104 to 106° F Temperature remains at its peak for a period of two to three hours then gradually fall to normal Between paroxysms the temperature may remain normal be subnormal or slightly elevated

A full course of treatment consists of from 10 to 12 paroxysms of fever above 103° F The minimum is six paroxysms and the maximum number that can be safely tolerated is 15 to 20 paroxysms The actual number of chills is not important Only those bouts of fever should be counted in which the temperature rises above 103° F The height of fever in any one paroxysm is less important for a successful therapeutic outcome than is the total number of hours of elevated temperature

Throughout the course of malaria the patient requires symptomatic medical treatment and must be observed carefully for complications The patient should be kept in bed during the febrile bouts but permitted to sit up in the interval when the temperature is normal The temperature should be recorded at intervals of two hours except during the paroxysms when it should be recorded every half hour The malaise and nausea can be controlled by hypodermic injections of codeine If the temperature ascends above 106 5° F it should be reduced by a tepid sponge bath or small doses of aspirin If the temperature remains constantly elevated if the paroxysms occur too frequently or if the patient is becoming unduly prostrated the fever can be temporarily interrupted by the intramuscular injection of thiobismol in amounts of 0 1 to 0 2 gm as suggested by Young McLendon and Smarr[17] This drug is of great value in reducing the frequency of paroxysms without eliminating them altogether The drug to be effective should be given approximately 18 to 20 hours after a paroxysm Oil soluble bismuth preparations should not be used because they will interfere with further febrile bouts Fever can also be interrupted temporarily in some cases by minute doses of quinine or one of the trivalent arsenicals These methods are more apt however to cause a complete cessation of fever Lightning pains

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have been treated to allow for any conclusion regarding the optimum dosage method of administration intravenously intramuscularly or intraspinously or the therapeutic effects There are as yet no adequate reports in the literature

A comprehensive cooperative investigation of the value of penicillin in neurosyphilis, including dementia paralytica is being carried out under the auspices of The National Research Council and The Office of Scientific Research and Development Evidence so far available indicates that penicillin has a high therapeutic effect on cases of meningeal neurosyphilis There is also evidence suggestive of benefit in the paretic form A reduction in cells and total protein in the spinal fluid occurs rapidly after a course of three to four million units of penicillin given by the intramuscular route A combination of fever and penicillin now being investigated may prove to be an advance in the treatment of dementia paralytica

Summary of Treatment — In summarizing the present situation regarding treatment paretic neurosyphilis may be modified beneficially in approximately one third to one half of the cases The most satisfactory method of treatment at the present time is fever therapy preferably malaria followed by chemotherapy for 2 to 3 years Long lasting remissions are obtained by this form of therapy and at the same time not infrequently there ensues complete serological recovery

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CHAPTER XXII

DISEASE OF THE NERVOUS SYSTEM IN CONGENITAL SYPHILIS

By C. WORSTER-DROUGHT

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Introduction

The classical works of Fournier, Hochsinger and Barlow ably demonstrated that serious organic disease of the nervous system frequently resulted from congenital or inherited syphilis. Even before the discovery of *Spirochæte pallida* by Schaudinn and Hoffmann in 1905, Casne 1896 had studied the spinal cords of 26 fœtuses born of syphilitic parents and found in four cases lesions identical with those of acquired neurosyphilis as well as more doubtful changes in seven other cases. Later Jullien was able to show that among 16[illegible] living infants the progeny of 43 syphilitic parents 50 per cent were attacked with meningitis and convulsive disorders. Ranke in 1908 carried out observations upon 60 brains of syphilitic fœtuses and infants and reached the conclusion that in their naked eye and microscopical characters the lesions in the nervous system were indistinguishable from similar affections in the adult due to acquired syphilis. By suitable methods the spirochæte often

As regards the frequency of definite involvement of the nervous system in congenital syphilis Jeans 1919 found abnormal cerebrospinal fluids in 32 7 per cent of 214 cases White and Veeder 1922 in 30 6 per cent of 206 cases and Stokes 1934 in 20 per cent of 150 cases In 202 cases of late congenital syphilis (tardive heredosyphilis) Stokes found some form of neurosyphilis in 20 per cent and mental retardation in 25 per cent Also of 150 cases investigated completely from a neurological stand point 26 per cent showed neurosyphilis

Apart from the production of gross pathological lesions it would appear that a common effect of congenital syphilitic infection is to inhibit bodily development and especially development of the central nervous system The result is bodily infantilism various grades of mental deficiency amentia or in some cases merely psychopathic or psychoneurotic manifestations The evidence for this assertion admittedly is difficult to adduce in precise terms Our knowledge of neuro-embryology and neuro physiology is too meagre to allow of more than hypothetical speculation as to the influence of syphilis upon the development and function of nerve cells Consequently we have largely to rely upon statistical and clinical evidence not altogether satisfactory sources for the reason that much depends on the personal views of the clinician as to syphilis as a causal factor and that further the cases seen and recorded by any single observer are too few for accurate statistical deductions This probably accounts for the wide variations met with in such statistics Koenig for instance as the result of his experiences asserted that the offspring of paretic patients often were idiots imbeciles the victims of infantile cerebral palsies and suffered from epilepsy and various other neuropathic ailments Although such conditions can result from inherited syphilis it is by no means the rule as the children of a neurosyphilitic parent or parents often are sound and healthy in appearance and yield negative Wassermann reactions In a series of 50 children (20 families) whose fathers were the victims of either tabes dorsalis tabo paresis or general paresis seen consecutively and investigated by the writer none showed any stigmata of congenital syphilis and only one showed a positive Wassermann reaction

In addition to infantilism mental deficiency and a psychopathic constitution some observers go so far as to say that various abiotrophies and dystrophies of the nervous system not ordinarily regarded as the result of syphilis are in reality due to an inherited syphilis which leads to premature degeneration of nervous tissue e g progressive muscular atrophy (motor neurone degeneration) paralysis agitans and even pre senile dementia

can be demonstrated in the nervous system of congenitally syphilitic still born infants as well as those dying shortly after birth In most cases the syphilitic infant owes the malady to being born of parents one or both of whom are suffering from syphilis this form is most commonly referred to as congenital syphilis but the terms inherited syphilis and heredosyphilis are used also Even an infant however may be the victim of acquired syphilis e g from a syphilitic wet nurse or from a mother infected after the birth of the child Lernier in 1909 showed how extra genital chancres could be acquired in a variety of ways by infants and children In such cases the character and subsequent course of the disease differs in no way from the inherited form

Congenital syphilis of the nervous system may be manifest at birth it may develop in early or late infancy in childhood or adolescence or in some instances at any age from 20 to 40 years It would appear in fact that no definite age limit can be placed upon the time when following apparent good health a latent congenital syphilis may not become activated in the form of a neurosyphilis In those cases that are late in developing symptoms it is usual to apply the term syphilis hereditaria tarda or tardive heredosyphilis With reference to this latent period there is no doubt that congenital syphilis can exist with no more than a positive Wassermann reaction to reveal its presence For instance F R Smith in 1933 investigated 462 cases of syphilis hereditaria tarda all over 13 years of age In no instance had the mother been treated for syphilis during pregnancy and according to the histories obtained manifestations of infantile syphilis were absent in nearly 90 per cent In 195 of the patients (42 per cent) the infection was latent The blood Wassermann reaction was positive in 92 per cent of the cases while in 182 free from any clinical manifestation of involvement of the nervous system examination of the cerebrospinal fluid showed typical pathological changes (asymptomatic neurosyphilis) in no less than ten (=10) per cent Consequently it would certainly appear that in the past too much stress has been laid upon the necessity for such stigmata as Hutchinson in teeth depressed nasal bridge rhagades etc to be present before a clinical diagnosis of congenital syphilis can be made At the same time however it must be pointed out that in many cases showing undoubted signs of inherited syphilis the serological reactions are negative In this connection J H Stokes 1934 found a pronounced age gradient of the Wassermann reaction towards the negative even more so than in the acquired form of the disease The first decade yielded positives in approximately 88 per cent 63 per cent in the second decade 46 per cent in the third and 15 per cent in the fourth decade

is a localized accentuation which results in a more definite clinical picture Apart from the posterior column degeneration of juvenile tabes however purely spinal cord manifestations are rare in inherited syphilis The spirochaete often can be demonstrated in the nervous system by appropriate staining methods

SYMPTOMATOLOGY

It has been shown conclusively that almost every form of adult neurosyphilis can be reproduced in inherited syphilis Consequently as regards the different clinical types of syphilis of the nervous system the same description applies to children as to adults Apart from juvenile paresis and juvenile tabes which justify separate descriptions only those forms of neurosyphilis met with either exclusively frequently or in some modified form in children will be considered in this section These include such conditions as cerebral arteritis leading to hemiplegia or convulsions meningitis hydrocephalus amentia affections of various cranial nerves and some cases of spastic diplegia and possibly some of idiopathic epilepsy In late congenital syphilis (tardive heredosyphilis) the order of frequency of clinical manifestations is as follows eye disease interstitial keratitis which occurs in 50 per cent of cases osseous lesions disorders of the central nervous system nerve deafness and affections of various cranial nerves

There would no doubt be a larger number of congenital syphilitic invalids but for the high rate of sterility miscarriages still births and short lived infants among those infected with syphilis Al o a generally reduced incidence of primary syphilis owing to the introduction of preventive measures as well as the modern vigorous treatment of infected prospective mothers has considerably reduced the frequency of congenital syphilis during recent years

Cerebral Arteritis

Cases have been reported in which syphilitic endarteritis and periarteritis have been the only cerebral lesions but in the majority of cases the arteritis is only part of a manifold syphilitic process affecting the mesodermic structures (meningo-vascular neurosyphilis) Endarteritis however may result in thrombosis and softening and when affecting the middle cerebral artery may be responsible for a spastic hemiplegia The hemiplegia usually is preceded by unilateral convulsions and epileptiform attacks may affect the paretic side when the hemiplegia

Third Generation Syphilis — Various authorities have differed as to the possibility of syphilis unto the third generation Fournier in 1891 reported several probable cases although he considered the occurrence infrequent while Jonathan Hutchinson in 1893 denied the existence of third generation syphilis The difficulty of deciding this question has no doubt been increased by the rarity of its occurrence as many of the victims of congenital syphilis are sterile while in others pregnancy results in abortions or the production of still born infants Also there is the uncertainty of excluding definitely acquired infection in the second generation member of the family Nevertheless there is good evidence that third generation syphilis does occur The most striking communication is that of Nabarro 1933 who personally observed 16 families with undoubted syphilis in three generations In undoubted cases Nabarro includes those in which a positive Wassermann reaction was found in grandparent parent and child and also cases in which the mother had definite stigmata of congenital syphilis such as Hutchinsonian teeth or interstitial keratitis He also reports a further seven probable instances in which there was an obviously congenital syphilitic mother and a child with an early suggestive history but a negative Wassermann reaction A striking example is recorded by A Elliott (1936) A positive Wassermann reaction was obtained in both the grandfather and the grandmother the latter showing signs of early general paresis Their daughter the mother yielded a positive Wassermann reaction but showed no clinical signs In the siblings of this generation one had interstitial keratitis and a positive Wassermann reaction three others being negative The mother gave birth to a female child and placental blood taken at the time of its delivery yielded a positive Wassermann reaction The child appeared healthy but showed a positive Wassermann reaction confirmed by repetition The writer also has met with three examples fulfilling the criteria of Nabarro s ' undoubted cases in two of these the third generation case suffered from juvenile paresis

Pathology

From the pathological standpoint the lesions of the nervous system in congenital syphilis are nearly always combined that is they include a variable combination of peri meso and endarteritis meningitis gummata and diffuse degenerative changes in the cells of the cerebral cortex basal ganglia and spinal cord In their macroscopical and microscopical characters these nervous system lesions of congenital syphilis differ in no way from those of the acquired disease Not infrequently however there

three to twelve months of birth and was present six times in fœtal life Nervous symptoms were absent in 11 cases but in others the symptoms were sleeplessness recurrent vomiting convulsions nystagmus and idiocy

Hydrocephalus in congenital syphilitics results either from involvement of the structures producing cerebrospinal fluid choroid plexus and ependyma or from obstruction of the foramina of the cerebral ventricles by chronic meningitis gummata or vascular enlargements Virchow and Jurgens described miliary gummata of the ependyma and Elsner has reported interstitial inflammatory changes of a specific character affecting the choroid plexus

Cerebral (Spastic) Diplegia

Infantile spastic diplegia is said to be an occasional manifestation of congenital neurosyphilis but is admittedly rare White and Veeder 1927 mention four examples in their series of 443 cases of congenital syphilis and Stokes 1934 found two in 200 cases an incidence of one per cent In numerous children suffering from cerebral diplegia the writer has found that less than one per cent has yielded a positive Wassermann reaction in either blood or cerebrospinal fluid The experience of Hobhouse 1932 has been similar as he found a positive Wassermann reaction in only a few cases and even in these the cerebrospinal fluid showed no clear evidence of an inflammatory reaction also the lesions showed no response to antisyphilitic treatment

Mingazzini has reported a group of cases reproducing the picture of family spastic paralysis

Spinal Cord Lesions of Meningo Vascular Type

Pure spinal cord syndromes apart from tabes dorsalis are admittedly rare in congenital syphilis For instance J Taylor 1905 mentions only that the spinal meninges may be involved but W Harris 1911 maintains that the spinal cord and its membranes may be affected soon after birth or later in life in the same way as in the acquired disease of adults Toyofuku 1910 studied the changes in the spinal cord of newborn syphilitic infants and found that pathological lesions were by no means infrequent Ranke 1908 described transverse myelitis (pia arachnitis with softening of the cord) and also recorded the case of a boy with spastic paraplegia improving on antisyphilitic treatment in whom a piece of excised liver showed typical pericellular cirrhosis Singer 1902 also reported acute paraplegia resulting from endarteritis and gummatous

for 3 to 5 days Subsequently the dose of hormone may be increased at a rate of 1 mgm at 5 day intervals with simultaneous decreases of 3 grams in the salt ration The continued administration of more than 10 mgm of desoxycorticosterone coincident with large doses of salt leads, at times to excessive retention of salt and water with complications discussed elsewhere

If an Addisonian patient is given adequate amounts of desoxycorticosterone salt need be given only according to taste On the other hand the daily requirement of hormone can be diminished appreciably, as is indicated in the above outline of treatment if the ingestion of sodium chloride is increased For example, a patient, whose desoxycorticosterone requirement is 6 mgm daily may be maintained in equally good health by the administration of 3 mgm of hormone supplemented by 6 grams of sodium chloride This is a point of practical importance for many patients because of economic reasons

A number of matters of detail concerning the subcutaneous administration of desoxycorticosterone deserve mention The patient should be taught to inject the hormone himself The anterior crural regions serve as the best site for injection, and the patient should be advised not to use the same site on repeated days The area should be massaged for 5 minutes after injection, this decreases the incidence of induration The patient, whose maintenance requirements of desoxycorticosterone acetate are being determined, should be weighed daily If the rate of gain, due primarily to salt and water retention after the first 3 days of treatment exceeds about one half a pound daily the dose of hormone or of salt should be reduced

Implantation Method — The treatment of hypoadrenalism by the implantation of pellets of desoxycorticosterone acetate has been developed chiefly by Thorn, and the following procedure is essentially that outlined by him Before pellets are implanted the maintenance dose is determined by subcutaneous administration as described above These patients during this time should receive a supplement of 3 or 4 grams of salt daily in addition to that of their diet The average time required for assay on this basis is about 4 weeks The patient then should resume activity for another month to be certain that the optimum dose has been determined as judged by the fact that the blood sodium remains at a normal level and clinical improvement is sustained Then one 125 mgm pellet of desoxycorticosterone acetate is implanted for each 0 5 mgm of hormone found to be required by daily injection The pellets are implanted subcutaneously in the infrascapular regions These pellets are effective in most patients for about one year When they have almost dissolved, symptoms of hypotension, anorexia and weakness gradually reappear New pellets may be implanted as these symptoms increase

The technique of manufacture of the pellets is of great importance If they are too soft they may crumble with the rapid absorption of hormone which

may result in severe overdosage On the other hand if they are packed too firmly the rate of solution may be markedly diminished and consequently their effect may be reduced

If satisfactory improvement does not take place after pellets are implanted the intake of sodium chloride should be increased Approximately 50 per cent of Thorn's patients who have had pellets implanted require a supplement of 3 or more grams of salt daily If symptoms of overdosage of cortical hormone appear pellets should be removed promptly Potassium chloride in doses of 1 5 grams daily may be given until the pellets are removed

Results —The results of desoxycorticosterone therapy are shown in part in Fig 2 The clinical improvement often is striking The majority of patients are restored to health compatible with earning their livelihood and the effects of this type of treatment upon the mortality rate have been commented upon The blood pressure increases slowly but the normal level may not be attained for many weeks in some patients despite improvement in other directions

It is the writer's opinion that supplements of 5 or 10 c c daily of the commercially available aqueous *extracts of the adrenal cortex* are of little or no benefit in the maintenance of the patient with Addison's disease These doses prevent hypoglycemia in the rat and dog but they are not of demonstrable value in man A lipo-extract of hog adrenal glands has been prepared and according to Ingle 1 c c contains the equivalent of about 4 mgm of corticosterone when assayed by the work capacity of the adrenalectomized rat This preparation in man demonstrates salt and water activity and can be shown to increase nitrogen excretion presumably as a result of its effect on protein metabolism It increases the subjective feeling of well being significantly in patients with Addison's disease

Treatment of an Adrenal Crisis —Adrenal crises develop in the course of Addison's disease at various times for reasons which have been discussed When a crisis appears vigorous therapy should be initiated at once Treatment should be directed towards the correction of (1) shock which is dependent upon a decrease in circulating blood volume and which results from loss of sodium salts and water and (2) the prevention of hypoglycemia The first of these disorders is corrected by the administration of salt and water in conjunction with desoxycorticosterone The second may be avoided by the repeated administration of glucose and at least theoretically by the liberal administration of adrenal cortical extract which is known to contain small quantities of steroids which increase gluconeogenesis or inhibit carbohydrate oxidation or both

The patient should be kept warm and a blood sample should be taken for the determination of sodium glucose non protein nitrogen and serum protein concentrations An infusion of 1 500 c c of 5 per cent glucose in 0 85 per cent sodium chloride solutions (not Ringer's solution) should be given immediately

This should be repeated depending upon the condition of the patient with particular emphasis upon the blood pressure as a criterion If the pressure remains below 80 mm Hg an infusion of 1,000 c c of plasma or a transfusion of blood should be given slowly or the infusion of glucose in saline should be repeated in 4 to 6 hours Even if the patient s condition is not critical the initial infusion should be repeated on the first day after 8 to 12 hours Following this a daily infusion should be given until vomiting has stopped the appetite is improved and the temperature has returned to normal If tuberculosis associated with fever is present infusions naturally are to be continued only until the blood sodium returns to approximately normal levels In patients, who develop hypoglycemia a hypodermoclysis of 1,000 c c of 5 per cent glucose solution injected with large amounts of novocaine may serve as a reservoir for sugar and may prevent a recurrence of hypoglycemia until small feedings of milk or diluted fruit juice with added sugar or lactose can be tolerated

In conjunction with the treatment with saline the patient in a crisis should be given 15 mgm of desoxycorticosterone intramuscularly immediately upon admission and 5 mgm more 6 and 12 hours later The sites of injection must be thoroughly massaged For the next two days 5 mgm of desoxycorticosterone may be given twice a day unless excessive fluid retention occurs Following this the patient s salt and hormone are adjusted as described for the maintenance of the patient

In a certain number of patients crises occur, which appear identical with those associated with the usual depletion of salt and water but the electrolyte pattern of the blood serum is found to be normal In these patients the blood pressure falls rapidly, the temperature rises abruptly without obvious cause and the patient frequently succumbs despite all therapy The nature of the disturbance in these patients is not clear but it may result from a disturbance in capillary permeability or in vasomotor regulation In the treatment of these individuals therapy with saline solution and desoxycorticosterone should be initiated as described above but after the first infusion and the first dose of desoxycorticosterone large doses of cortical extract should be administered at frequent intervals without further recourse to saline solution and desoxycorticosterone particularly in the absence of hemoconcentration Twenty to thirty c c of cortical extract should be injected intravenously and the patient should receive doses of 10 c c of cortical extract every 1 or 2 hours until the blood pressure rises above shock levels, and the temperature falls Transfusions of plasma or whole blood may be tried if progress is not satisfactory but the results usually are disappointing

In the opinion of the writer *injections of epinephrine* have no influence upon the outcome of the Addisonian crisis but they do not appear to have an adverse effect when given in small doses

Complications of Desoxycorticosterone Therapy — The effects of excessive doses

of desoxycorticosterone in the normal dog have been discussed elsewhere In patients with Addison's disease excessive dosage results in (1) edema and at times generalized anasarca (2) congestive heart failure and (3) arterial hypertension

Extensive *edema* not infrequently was observed in the early days of desoxycorticosterone therapy when large doses of the hormone and salt were given over rather prolonged periods of time With the plan of therapy outlined above the appearance of significant edema is distinctly unusual If edema does appear it is controlled readily by a reduction in the intake of sodium salts or by a reduction in dosage of desoxycorticosterone in patients not receiving supplementary sodium chloride medication

Cardiac insufficiency like anasarca is today a complication rarely encountered in the course of desoxycorticosterone therapy It appears to result from a combination of an increase in plasma volume increase in arterial pressure and a decrease in concentration of potassium in the blood serum with a slight but similar decrease in the potassium of heart muscle cells in dogs Darrow has demonstrated histopathological lesions in the heart muscle of normal rats receiving large doses of desoxycorticosterone over long periods of time Similar changes do not develop regularly in man The heart of the Addisonian patient is unusually small before treatment It returns to normal with well controlled therapy and dilates only if excessive salt and desoxycorticosterone are administered When heart failure occurs it is associated usually with dyspnea orthopnea pulmonary congestion and an increase in venous pressure On the other hand sudden death apparently of cardiac origin but without congestive failure is encountered occasionally in patients who have received large amounts of hormone Cardiac insufficiency should be treated by the cautious reduction in the dosage of hormone and salt Digitalis should be used as in other types of congestive failure

Arterial hypertension as stated elsewhere appears rather frequently in patients treated with desoxycorticosterone after 6 months to a year of treatment If the pressure does not exceed 150/90 little cognizance need be taken of this complication In patients who have had hypertensive disease prior to the onset of Addison's disease the reappearance of significant hypertension may occur In patients who develop hypertension an attempt should be made to reduce the dose of salt or hormone or both without inducing manifestations of hypoadrenalism

Occasionally *contractures of the lower extremities* appear in patients receiving desoxycorticosterone therapy but it has not been demonstrated that these develop as a consequence of treatment with this hormone

Intercurrent infection constitutes a serious complication in Addison's disease perhaps because of failure of the immune mechanism as suggested by White and Dougherty and it commonly induces crises which not infrequently prove fatal When infection accompanied by fever occurs the patient should be hospitalized

This should be repeated depending upon the condition of the patient with particular emphasis upon the blood pressure as a criterion If the pressure remains below 80 mm Hg an infusion of 1 000 c c of plasma or a transfusion of blood should be given slowly or the infusion of glucose in saline should be repeated in 4 to 6 hours Even if the patient's condition is not critical, the initial infusion should be repeated on the first day after 8 to 12 hours Following this a daily infusion should be given until vomiting has stopped the appetite is improved and the temperature has returned to normal If tuberculosis associated with fever is present, infusions naturally are to be continued only until the blood sodium returns to approximately normal levels In patients, who develop hypoglycemia a hypodermoclysis of 1 000 c c of 5 per cent glucose solution injected with large amounts of novocaine may serve as a reservoir for sugar and may prevent a recurrence of hypoglycemia until small feedings of milk or diluted fruit juice with added sugar or lactose can be tolerated

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Complications of Desoxycorticosterone Therapy — The effects of excessive doses

identical with that of the surgical patient or of an Addisonian patient with in fection

Climate

Addisonian patients are particularly susceptible to extremes of heat and cold Crises are especially common during hot weather and may be precipitated by physical exercise associated with profuse sweating with consequent loss of sodium salts and water During hot weather patients should drink more water and increase their consumption of salt perhaps 2 or 3 grams if sweating is profuse They should be advised to avoid undue exertion at these times Many Addi sonian patients feel the cold intensely and should dress accordingly in winter Adrenalectomized animals die quickly when subjected to ice box temperatures perhaps because they are unable to convert protein to carbohydrate adequately under this form of stress

Pain and Mental Reaction

It is the impression of the writer that painful stimuli augment the manifesta tions of adrenal insufficiency and that for this reason they should be avoided as far as possible In most Addisonian patients codein is particularly well tolerated and should be used freely for the control of pain

Anxiety often intensifies anorexia nausea and gastric intolerance in the patient with Addison s disease For example in one of the writer s patients a university professor a fatal crisis appeared to be initiated by worry over a severe financial reversal

WATERHOUSE FRIDERICHSEN SYNDROME

For many years there have appeared in medical literature case reports of patients presenting a clinical picture which has come to be known as the Water house Friderichsen syndrome This disease picture usually is encountered in infancy or early childhood but is seen also in adults It deserves brief considera tion in this section since some of the manifestations may be ascribed to *acute cortical adrenal insufficiency* The Waterhouse Friderichsen syndrome is charac terized in most cases by the abrupt onset of fever headache delirium or convul sions nausea and vomiting These symptoms are associated with the development of a generalized purpuric rash in which the lesions vary from 1 mm to more than 1 cm in diameter Marked peripheral cyanosis appears as the disease progresses and the blood pressure falls to shock levels Patients usually succumb in 24 to 72 hours with the picture of profound circulatory collapse Extensive hemorrhage into the adrenal glands as determined at autopsy constitutes an integral part

at once, and an infusion of glucose in saline solution should be given immediately Desoxycorticosterone or cortical extract should be given as in a crisis Penicillin or sulfadiazine should be given at once and in full dosage whenever the infectious agent is one likely to respond to this type of therapy

It must be reemphasized that tuberculous infection is present in the majority of patients suffering from hypoadrenalism In these patients the treatment of tuberculosis constitutes an independent and important problem

Surgery in Hypoadrenalism

Surgical procedures particularly when associated with the administration of a general anesthetic precipitate serious and frequently fatal crises The introduction of desoxycorticosterone has reduced operative mortality appreciably in Addisonian patients Nevertheless the surgical risk is great and only the most essential operative procedures should be undertaken e g operations for acute appendicitis, operations for mastoiditis and nephrectomy for tuberculosis, etc Whenever possible surgical procedures should be carried out under local anesthesia When a general anesthetic is necessary, cyclopropane or open ether are to be preferred

If operation can be delayed with safety, the patient should be given 10 mgm of desoxycorticosterone subcutaneously and an infusion of 1,500 c c of 5 per cent glucose in 0 85 per cent sodium chloride solution 6 hours before operation The infusion should contain in addition 40 c c of cortical extract At the time of operation before anesthesia is started, this treatment should be repeated or 500 to 1 000 c c of plasma may be given After operation the blood pressure should be followed at least every 2 hours and the same vigilance should be exercised as in the treatment of a crisis Desoxycorticosterone should be given in doses of 10 mgm daily and 20 c c of cortical extract should be given subcutaneously or intramuscularly at 4 to 6 hour intervals for 2 or 3 days Infusions should be repeated at 12 hour intervals if progress is not satisfactory

Pregnancy in Addison's Disease

The severity of Addison s disease may be intensified in the first 3 months of pregnancy by nausea and vomiting In the latter half of the period of gestation the disease may possibly be ameliorated by the secretion of the fetal glands and by the liberation of sex hormones which have been shown by Thorn and others to increase the retention of the sodium ion and water At the time of delivery and in the first 2 or 3 days postpartum a serious and often fatal crisis may result from loss of fluid and blood as well as of progesterone and also circulating cortical hormone from the fetus The treatment of the patient at the time of delivery is

fusion glucose in saline infusions desoxycorticosterone and cortical extract made a complete recovery without evidence of residual adrenal cortical insufficiency The part played by adrenal cortical therapy in the recovery of this patient obviously is wholly speculative It is conceivable that the chemical changes in the blood were nonspecific Nevertheless it seems proper in view of the demonstrable effects of infection on activity of the adrenal cortex to employ adrenal cortical replacement therapy in combination with specific chemotherapy for the underlying sepsis

Hypoadrenalism in Hemorrhage Traumatic Shock and Burns

The loss of a small amount of blood mild trauma and burns even small in area prove rapidly fatal to adrenalectomized animals The resistance of these animals to the injuries described is greatly enhanced by preliminary treatment with large doses of adrenal cortical extract As has been indicated animals and human subjects suffering from adrenal cortical insufficiency present numerous symptoms and signs identical with those present in the states of shock Furthermore the adrenal glands in fatal traumatic shock hemorrhage and burns show certain characteristic changes On the basis of these facts numerous experimental and clinical studies have been undertaken to determine the possible therapeutic value of adrenal cortical hormones in the disorders mentioned At the present time no convincing evidence has been adduced to indicate that the adrenal cortical hormones available have any significant value in the treatment of hemorrhage traumatic shock or burns in patients or in any but adrenalectomized animals

Hyperfunction of the Adrenal Medulla

Tumors of the medullary portion of the adrenal glands include gangliomata neuroblastomata and pheochromocytomata The first two of these are not associated with disturbances of adrenal function On the other hand the pheochromocytoma or paraganglioma induces in many instances a characteristic and dramatic clinical picture which results from the intermittent discharge of epinephrine into the blood stream

Pheochromocytomata may occur at any age but develop as a rule between the ages of 30 and 60 years They occur a little more frequently in females than in males The tumors vary considerably in size but are in most instances 2 to 4 cm in diameter and consequently can not as a rule be detected on physical examination The tumors arise most frequently from the pheochrome cells within the medulla of one adrenal gland In rare instances they develop in both glands Pheochromocytomata are found also arising from pheochrome cells in conjunction with the sympathetic ganglia elsewhere They have been reported also in the

of the syndrome but the syndrome may occur without the appearance of hemorrhage in the glands This syndrome is described also in Vol V, Chapt IV-A of Oxford Medicine

The Waterhouse Friderichsen syndrome develops as the result of overwhelming infection by any one of a variety of microorganisms The majority of cases are due to meningococcal infection, usually without meningeal involvement but the syndrome has been reported also in severe diphtheria and in sepsis caused by hemophilus influenza the pneumococcus, hemolytic streptococcus, etc It is believed also that a number of cases develop as a result of thrombocytopenic purpura In some of these cases however sepsis with depression of the circulating platelets may be mistaken for primary thrombocytopenia

In most instances the syndrome escapes recognition or the course is too rapidly fatal to permit studies which might help to clarify the role of hypoadrenalism in the state of collapse which terminates the disease However in one patient with fulminating meningococcus sepsis who presented the classical symptoms and signs of the Waterhouse Friderichsen syndrome chemical studies of the blood at the Presbyterian Hospital revealed the following information The serum sodium concentration was 122 9 milli equivalents per liter, the blood sugar was 50 mgm per 100 c c and the blood urea nitrogen was 58 mgm per 100 c c These changes are typical of cortical adrenal insufficiency and at autopsy extensive hemorrhage was found throughout both adrenal glands

The *treatment* of the Waterhouse Friderichsen syndrome should be directed toward (1) the control of infection and (2) the treatment of possible hypoadrenalism Penicillin or sulfadiazine should be used promptly and in full dosage The possible hypoadrenalism should be treated as an adrenal crisis In the case described above the level of sulfadiazine was maintained at 18 mgm per cent The patient was given repeated infusions of 5 per cent glucose in saline She was given 10 mgm of desoxycorticosterone upon admission and 5 mgm 6 and 12 hours later She received 40 c c of adrenal cortical extract intravenously and intramuscular injections of 10 c c of extract at frequent intervals Despite this therapy the patient, after temporary improvement became comatose, cyanosis increased and she died suddenly 72 hours after admission It is obvious that despite intensive and specific therapy treatment may be of no avail when the disease picture is well established It seems probable that generalized and irreversible tissue damage resulting from overwhelming infection was of greater importance in contributing to the fatal outcome of the Waterhouse Friderichsen syndrome in this patient than was acute cortical adrenal insufficiency In another patient with meningococcus sepsis and shock depression of the serum sodium to 121 m eq per l lowering of the blood sugar to 56 mgm per 100 c c and elevation of the urea nitrogen to 29 mgm per 100 c c were noted on admission to the Presbyterian Hospital This patient treated with penicillin sulfadiazine, trans

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carotid body In a boy of 12 years seen at the Presbyterian Hospital a large pheochromocytoma associated with intense and persistent hypertension was found in the adductor canal of the right thigh Epinephrine has been isolated from pheochromocytomata arising both within and without the adrenal glands on a number of occasions Pressor effects have not been observed in the tumors arising from the carotid body A large majority of pheochromocytomata are benign in character, but they may be malignant The malignant tumors rarely elaborate epinephrine

Clinical Picture — The clinical picture of hyperepinephrinism, as it occurs in association with pheochromocytomata, was described first by Labbe in 1922 The syndrome is characterized by terrifying and unpredictable episodes which vary from less than a minute to 1 or 2 hours in duration The sensations which the patient experiences as well as the objective findings, are those which ordinarily result from the injection of a large dose of epinephrine In the typical case the patient, either at rest or in association with some physical activity, is seized suddenly with a sense of constriction which often begins in the legs and arms and rapidly spreads to the epigastrium and the precordium This is followed quickly by a choking sensation The patient complains of terrific pounding of the heart and a throbbing headache, often associated with blurring of vision Nausea and vomiting occur frequently and the patient is aware of a coarse, uncontrollable tremor These symptoms are accompanied by a sense of great apprehension During the attacks there is striking pallor, the extremities are cool, the pupils tend to dilate, respiration is exaggerated there is usually an increase in pulse rate but bradycardia may be present The heart is over active, and in individuals with underlying heart disease pulmonary edema may develop The blood pressure rises during the attack, and the height of the pressure varies with the severity of the episode The systolic pressure, usually normal between attacks may rise to 300 mm Hg The diastolic pressure does not, as a rule, show a corresponding increase The blood sugar frequently rises in an attack from normal values to 160 to 200 mgm per 100 c c if the episode lasts for some time The hyperglycemia often is accompanied by transient glycosuria The attacks often are followed by a feeling of complete exhaustion which may last for many hours

The attacks usually are entirely irregular in their frequency even in the same individual Thus in one patient seen by the writer 4 attacks occurred in the course of 2 months and then the patient was entirely free from symptoms for 10 months Following this attacks increased in frequency, and in the course of the next year they occurred oftener than once a week The intensity of the attacks like their frequency is extremely variable and probably depends upon the amount of adrenalin discharged from the tumor at the time

In a few instances pheochromocytomata from which epinephrine can be extracted are associated with the presence of persistent rather than paroxysmal

hypertension The following record of a patient of Dr D W Atchley seen recently at the Presbyterian Hospital serves as an example The patient was a 29 year old unmarried school teacher whose blood pressure was found 2 years before admission to be 200/110 From that time on her pressure was persistently elevated while ambulatory and during a period of observation at another hospital 1 year before admission At that time when an attempt was made to ascertain the mechanism of her severe and sustained hypertension she complained of soreness in the right side of her abdomen and thought that a lump could be palpated For the year prior to admission she suffered from mild recurrent frontal headaches For 6 weeks before coming to the hospital she had had progressive failure of vision At no time had she had significant emotional disturbances nor had she ever experienced an episode suggestive of hyperepinephrinism On ophthalmoscopic examination the significant findings included mild but definite papilledema narrowing of the retinal arterioles old hemorrhages and exudate Her arterial pressure varied between 248/150 on admission and 200/100 after prolonged rest A fixed tender mass the size of a lemon was palpated to the right of the umbilicus At operation it was found to be attached to the vena cava During the manipulation of this mass in the process of its removal her blood pressure rose abruptly to 300/160 After almost complete removal of the mass the patient made an uneventful recovery and in the next 3 weeks her blood pressure at no time exceeded 145 mm Hg systolic or 100 diastolic The tumor proved to be a typical pheochromocytoma and preliminary pharmacological study has revealed the presence of a pressor substance presumably epinephrine

Diagnosis

The similarity of the state of panic which may occur in psychoneurotic patients under strain and attacks of hyperepinephrinism is apparent Consequently in patients with a history of marked emotional instability and a labile blood pressure the diagnosis of pheochromocytoma may be impossible or may become apparent only after a prolonged period of observation When however the typical disease picture appears suddenly and without warning in a patient without a background of instability the nature of the episodes should suggest at once the possible presence of a pheochromocytoma Careful observation of the sequence of events in an attack may help to differentiate an emotional panic from the hyperepinephrinism resulting from a *pheochromocytoma* Thus in the former the elevation of blood pressure heart consciousness and development of *tremor follow the feeling of panic which results from a psychogenic stimulus* In the patient with a pheochromocytoma the feeling of apprehension develops with the attack *Furthermore in most instances the objective manifestations of* hyperepinephrinism are greater than in the emotional state

In contrast to patients with hypertensive vascular disease it might be expected that patients with a pheochromocytoma would exhibit a decrease in skin temperature and a decrease in peripheral blood flow, characteristic of the action of epinephrine Evans and Stewart have observed just these changes in a patient studied by them One year after the removal of the pheochromocytoma they found an increase in the average skin temperature and in the peripheral blood flow These authors emphasize the fact that, whereas the average temperature of the hands and feet is decreased by the epinephrine secreted, there may be poor correlation between the skin temperature in the extremities and the average skin temperature at any one time

In a certain number of cases the diagnosis can be substantiated by the perirenal injection of oxygen by which the contours of the adrenal glands are made visible roentgenographically The presence of a tumor, which can not be palpated may become apparent with this procedure When a mass can be palpated in the abdomen and intermittent or persistent hypertension is present the mass may be massaged cautiously in order to reproduce evidence of hyperepinephrinism In the absence of a palpable mass or the demonstration of a tumor by perirenal air injection exploration to establish the diagnosis is often futile as the tumors may be multiple and may arise outside the adrenal glands but nevertheless is justifiable

Prognosis

The prognosis of patients with hyperepinephrinism is variable The disease may go on for many years with only occasional attacks On the other hand a patient may die during an episode particularly when associated with pulmonary edema

Treatment

Surgical removal of the tumor constitutes the basis of treatment This procedure carries with it however considerable risk Manipulation of the tumor in the process of its removal may cause the discharge of epinephrine with a serious rise in arterial pressure A number of patients have died suddenly during operation possibly as a result of ventricular fibrillation or acute cerebral ischemia During episodes of hyperepinephrinism sedatives should be administered and the patient should be placed in the semirecumbent position, if respiratory distress appears

Hyperfunction of the Adrenal Cortex

Hyperactivity of the adrenal cortex is associated with certain tumors of the cortex which usually are malignant and also with hypertrophy of the adrenal

glands which commonly is termed hyperplasia More frequently the disturbances which are ascribed to overactivity of the adrenal cortex are encountered in individuals who have no demonstrable gross or histopathological changes in the glands Hyperfunction of the adrenal cortex is manifested by two groups of disorders *in which the physiological and clinical disturbances appear to result from* the liberation of different steroids These two forms of hyperadrenalism are known as the *adrenogenital syndrome* and *Cushing s syndrome* Whereas the characteristics of each in pure form are fairly distinct in many instances certain manifestations of both syndromes occur in the same individual

Adrenogenital Syndrome

The adrenogenital syndrome as stated by Wintersteiner comprises all conditions in which the abnormal changes in the sexual sphere are referable to organic or functional disturbances in the adrenal cortex The incidence of the *syndrome is far higher in females than in males and in the former is characterized* by the appearance of the secondary sex characteristics of the male with regression of the female characters In males the adrenogenital syndrome is characterized in children by precocious puberty and herculeanism and in adults it may result in a tendency toward feminization The age at which the adrenogenital syndrome develops is of the greatest importance in determining the degree of physiological and clinical change effected in the individual As a general rule it may be said that the earlier the onset in a patient the greater will be the deviation from normal development and appearance It is also of importance to recognize that the degree of physiological and clinical abnormality brought about by the adrenogenital syndrome bears no relation to the nature of pathological change in the glands Thus there may *be none of the usual manifestations of* the adrenogenital syndrome in a patient with a large and malignant tumor of the cortex and on the other hand the most extensive disturbances may appear without any demonstrable anatomical abnormality in these structures

It appears to be well established that the adrenal cortex is capable of elaborating both androgenic and estrogenic substances probably in response to chemical stimuli from the pituitary gland The significance of this type of activity in the adrenal glands under normal conditions is not apparent since the cessation of 17 keto-steroid excretion in the female with hypoadrenalism and a striking decrease in males with Addison s disease are not attended by any effect on the sexual activity of the individual Furthermore changes in growth and development which characterize the adrenogenital syndrome cannot be reproduced in animals by the injection of extracts of the adrenal cortex On the other hand certain of these changes can be simulated in young animals by the injection of androgenic or estrogenic substances and abnormalities can also be induced in the fetus by their

injection into pregnant animals It seems likely therefore that the development of the adrenogenital syndrome may be related (1) to excessive elaboration of normal or abnormal androgenic or estrogenic substances by the adrenal glands (2) to an abnormal degradation of adrenal steroids into active androgenic and estrogenic material possibly by the liver (3) to an increased responsiveness of certain body tissues to small amounts of normal or abnormal steroids elaborated by the adrenals or (4) to the elaboration of estrogenic or androgenic substances by other tissues e g arrhenoblastomata or granulosa cell tumors of the ovary

In the majority of patients exhibiting the adrenogenital syndrome there is an increase in the androgen content of the urine whether the syndrome develops in association with a cortical tumor or with hyperplasia, or whether it develops without anatomical change in the glands The nature of the androgenic material recoverable from the urine from patients with the adrenogenital syndrome varies and as already stated it may represent an abnormal steroid elaborated by the adrenal glands or an abnormal degradation product of a normal substance In a case reported by Dorfman and Schiller, an androgenic substance, androstenol 3 (α) 17 one was recovered from the urine The same material was isolated from the urine of another patient by Wolfe Fieser and Friedgood This androgenic compound showed no adrenal cortical activity when assayed in adrenalectomized rats In a number of cases the excretion of 17 ketosteroids may not exceed the accepted normal limits In these patients it is possible that the active principle is not eliminated in the ketonic form In other cases as stated elsewhere the individual may be unusually responsive to the normal steroids possibly on the basis of genic abnormalities Infrequently tumors of the adrenal cortex giving rise to the adrenogenital syndrome are associated with excessive excretion of estrogens instead of androgens

The adrenogenital syndrome may develop in utero or shortly after birth In female children of this age group the disease may possibly appear because of transmission of an excess of normal steroids from the maternal circulation The syndrome may develop also without any abnormal chemical stimulus from the mother In these infants the degree of deviation of the sex development from the normal is variable There may be only slight enlargement of the clitoris but more frequently well marked *pseudohermaphroditism* is present The clitoris may resemble a large penis there may be atresia or absence of the vagina and the internal genital organs may be quite rudimentary so that doubt may arise concerning the true sex In the male the appearance of the adrenogenital syndrome in utero or in infancy may result in pseudohermaphroditism with hypospadias and other changes simulating the external genitalia of the female if the disturbances in the steroid metabolism of the mother or fetus leads to the excessive production of estrogens

The excessive elaboration of androgens regardless of the basic cause i e, tumor etc in early childhood leads to excessive masculinization in both females and males In both sexes pubic and body hair appears frequently before the age of ten years the voice deepens acne appears on the face there is an unusual degree of muscular development the epiphyseal and dental development is accelerated and these children are extraordinarily alert mentally In the female the clitoris enlarges and in the male the genitalia are overdeveloped Sexual maturity appears in early childhood in males and menstruation may never appear in females This syndrome commonly is known as *adrenal virilism*

The appearance of the adrenogenital syndrome after puberty in the female is associated with a reduction or total cessation of the menses flattening of the breasts the development of hirsutism the appearance of acne deepening of the voice as a result of lengthening of the vocal cords and loss of normal libido In males the appearance of the adrenogenital syndrome is recognized only in those instances in which a tumor of the cortex is associated with the elaboration of estrogenic substances and a tendency toward feminization associated with enlargement of the breasts and hips and loss of libido

Diagnosis of Adrenogenital Syndrome — The appearance of the adrenogenital syndrome should lead to the suspicion of an adrenal cortical tumor or hyperplasia of the adrenal glands even though these abnormalities are present only occasionally Procedures which aid in the establishment of the diagnosis are (1) the determination of the 17 ketosteroid and estrogen excretion in the urine and (2) perirenal insufflation with oxygen to demonstrate roentgenographically the size and contours of the adrenal glands When doubt exists it may be justifiable to explore both adrenal glands It must be recognized that the adrenogenital syndrome may be simulated by virilizing tumors of the ovary e g arrhenoblastomata and granulosa cell tumors and that these must be excluded if possible by pelvic examination

Treatment — The treatment of the adrenogenital syndrome is surgical in cases in which tumor or definite adrenal hypertrophy is present Unfortunately the great majority of adrenal cortical tumors responsible for the syndrome are malignant although in certain instances the tumor can be diagnosed and removed before metastases occur In females who have reached puberty excision of the tumor may result permanently or temporarily in (1) re-establishment of menses (2) enlargement of the breasts (3) an increase in libido (4) a return of the voice to normal (5) the disappearance of acne (5) a decrease in 17 ketosteroid excretion and (7) some decrease in hirsutism Unfortunately the excess of facial hair, which constitutes one of the most distressing developments in these patients regresses but slightly in most instances In patients with significant bilateral adrenal enlargement without tumor resection of a portion of one or both glands usually brings about temporary alleviation of the disturbances mentioned In

the prepubertal group of patients with adrenal virilism the same diagnostic procedures and surgical treatment are indicated In addition, amputation of the enlarged clitoris and plastic operative measures may correct to some degree the anatomical abnormalities

In patients who are to undergo removal of an adrenal cortical tumor, or who are to have resection of an hypertrophied gland preoperative and postoperative treatment similar to that outlined for patients with Addison's disease is indicated In most of these patients there is comparatively little risk of acute adrenal insufficiency as compared with patients suffering from Cushing s syndrome, but this precautionary therapy nevertheless should be employed

In patients with the adrenogenital syndrome, in which tumor and hypertrophy of the glands have been excluded there is no treatment other than that which may be accomplished by plastic surgery or estrogenic therapy

Cushing s Syndrome

Cushing s syndrome was described first by Harvey Cushing in 1932 as a clinical entity which he found to be associated with basophilic adenomata of the pituitary gland Since the original observations made by Cushing it has been established that this syndrome usually appears without the presence of a basophilic adenoma of the pituitary Indeed it is most frequently associated with tumors of the adrenal cortex or hypertrophy of the adrenal glands and occasionally with tumors of the ovary It has been described also in association with thymic tumors and in a number of instances no tumors of endocrine structures have been found post mortem In almost all cases there appears hyalinization of basophilic cells in the hypophysis This was emphasized first by Crooke and it was suggested by him that this change might be related to the underlying mechanism involved in the development of the syndrome Heinbecker ascribes the development of Cushing's syndrome in a number of patients without either tumor or hyperplasia of the adrenal cortex to degeneration of the hypothalamic paraventricular nuclei This lesion is associated with Crooke s changes in the basophiles of the anterior lobe of the pituitary In these patients Heinbecker believes that Cushing s syndrome arises from an increase in responsiveness to the steroids normally elaborated by the adrenal cortex Experimental evidence believed to support this view is not wholly convincing The diversity of the disorders with which Cushing s syndrome or pituitary basophilism' may be associated suggests more than a single etiological basis It seems probable however that in all instances it may be referable either to over production of adrenal steroids or over responsiveness to normal secretions

Cushing s syndrome in most instances is associated with chemical, physiological and clinical disturbances which suggest hyperfunction of the adrenal cortex

In the adrenogenital syndrome as has been mentioned the disturbances present cannot be reproduced by the injection of adrenal cortical extract but can be simulated in part by the administration of androgenic and estrogenic hormones In Cushing s syndrome there is often an excessive excretion of 17 ketosteroids as in the adrenogenital syndrome but in addition more characteristic evidence of hyperfunction of the adrenal cortex usually is present Thus the concentration of the sodium in the blood serum is increased in many cases from the normal level of about 140 m eq per liter to 145 m eq per liter whereas the concentration of potassium may be reduced to about 3 5 m eq per liter These changes are both qualitatively and quantitatively similar to those induced in normal dogs by the prolonged administration of desoxycorticosterone Furthermore the tendency to lose nitrogen and the tendency to hyperglycemia and glycosuria resemble the effects produced either by the administration of cortical extract or steroids of the type of 17 hydroxy 11-dehydro-corticosterone to normal or partially pancreatectomized animals These effects can be induced also by the injection of anterior pituitary extract with its known diabetogenic activity Whereas these effects on carbohydrate and protein metabolism indicate that one action of these hormones is to convert protein into carbohydrate the assumption that this is the basis for the disturbances present in Cushing s syndrome lacks support It has been suggested by Albright that an excess of some cortical steroid which inhibits protein synthesis is responsible for many of the changes present in Cushing s syndrome This viewpoint which has much in its favor has not been established with any measure of certainty

Clinical Picture of Cushing s Syndrome — The clinical picture presented by patients with Cushing s syndrome is both striking and characteristic The syndrome occurs much more frequently in females than in males It may occur at any age but in contrast to the adrenogenital syndrome which usually appears under the age of 30 Cushing s syndrome is seen most frequently in women between the ages of 30 and 50 years The onset of the syndrome usually is insidious and the rate of progression is variable

The outstanding feature of Cushing s syndrome is the change which it effects in the appearance of the individual There is a tendency for the patient to become mildly or moderately obese although the distribution of fat and relaxation of the abdominal wall suggest a great gain in weight The cheeks become firm and shiny and tend to protrude giving a truly porcine expression The neck becomes thickened and appears short because of submental obesity The thorax and abdomen and hips also are sites of fat deposition The breasts become pendulous and the abdominal wall becomes relaxed protruberant and also pendulous There is little if any change in the distal portion of the extremities At times the changes in configuration of the patient take place without gain in weight The patients develop a plethoric and cyanotic hue suggestive of polycythemia which however

sat at home without interest or occupation She became mentally dull and introspective Her appearance assumed the characteristics of Cushing's syndrome She presented also the usual laboratory and x ray findings In the course of a year following the removal of an adenoma of the right adrenal gland by Dr George F Cahill the physical characteristics of her disease disappeared and she had a complete change in personality (Fig 4) She became quite gregarious and returned to a full time gainful occupation Unfortunately, many of the adrenal cortical tumors which give rise to Cushing's syndrome, are malignant, and fatal recurrence often follows temporary alleviation of the syndrome

In the absence of demonstrable neoplasia and in patients in whom there is no obvious hyperplasia of the adrenal cortex two types of treatment may be employed Radiation of the pituitary or adrenal glands has been employed with some improvement in a number of patients It is possible that the benefit noted may have resulted from spontaneous remission in the disease process Albright recently has described striking improvement in a number of patients as a result of continued treatment with 25 mgm of testosterone or methyl testosterone daily In these patients Albright has reported increase in strength associated with the establishment of a positive nitrogen, phosphorus and calcium balance There has been an increase in deposition of calcium in the bones, the facial contours have reverted toward normal and the plethoric appearance has decreased In contrast to the salutary effects reported is the acceleration of growth of facial and body hair The ultimate results of this type of treatment are not yet established Most patients with Cushing's syndrome live less than ten years

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sat at home without interest or occupation She became mentally dull and introspective Her appearance assumed the characteristics of Cushing s syndrome She presented also the usual laboratory and x ray findings In the course of a year following the removal of an adenoma of the right adrenal gland by Dr George I Cahill the physical characteristics of her disease disappeared and she had a complete change in personality (Fig 4) She became quite gregarious and returned to a full time gainful occupation Unfortunately, many of the adrenal cortical tumors which give rise to Cushing s syndrome are malignant, and fatal recurrence often follows temporary alleviation of the syndrome

In the absence of demonstrable neoplasia and in patients in whom there is no obvious hyperplasia of the adrenal cortex two types of treatment may be employed Radiation of the pituitary or adrenal glands has been employed with some improvement in a number of patients It is possible that the benefit noted may have resulted from spontaneous remission in the disease process Albright recently has described striking improvement in a number of patients as a result of continued treatment with 25 mgm of testosterone or methyl testosterone daily In these patients Albright has reported increase in strength associated with the establishment of a positive nitrogen phosphorus and calcium balance There has been an increase in deposition of calcium in the bones the facial contours have reverted toward normal and the plethoric appearance has decreased In contrast to the salutary effects reported is the acceleration of growth of facial and body hair The ultimate results of this type of treatment are not yet established Most patients with Cushing s syndrome live less than ten years

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CHAPTER XIV

ENDOCRINE FUNCTIONS OF THE HYPOPHYSIS

By HARRY B FRIEDGOOD

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Part I

ANATOMY EMBRYOLOGY AND PHYLOGENY OF THE HYPOPHYSIS CEREBRI

Introductory Remarks

An adequate conception of the clinical and functional pathology of the hypophysis cannot be achieved other than through precise information concerning the morphological structure and anatomical relations of the constituent parts of this endocrine organ A systematic nomenclature which is based on functional as well as morphological considerations, is a very important aspect of this view point

There was a time during the development of notions concerning hypophysial structure when anatomists and clinicians alike referred to the anterior and posterior lobes of the hypophysis with apparent morphological and functional specificity Neither this terminology nor the viewpoint which fostered it appears to be tenable any longer Numerous studies especially those of Tilney have introduced a more significant conception of the morphology and therefore of the physiology and pharmacology of the hypophysis These topographical observations have disclosed that the so-called anterior and posterior lobes are each composed of several subdivisions which are neither in the anterior nor posterior position respectively In the literature the term anterior lobe refers quite generally to the pars distalis of the adenohypophysis whereas the designation posterior lobe is equivalent to the processus infundibuli of the neurohypophysis

The subdivisions of the adenohypophysis include the pars distalis pars intermedia pars infundibularis and the pars tuberalis and the neurohypophysis has been subdivided into the processus infundibuli pediculus infundibularis bulbus infundibularis and labrum infundibularis or median eminence of the tuber cinereum (Fig 1) With the exception of certain neurophysiologists who have been concerned with the experimental study of this region relatively recently few investigators have paid much attention to the functional importance of these subdivisions Most physiological and pharmacological experiments have been aimed either at the 'anterior" or posterior lobe Perhaps a majority of the conflicting and mutually incompatible observations which are recorded in the literature can be attributed to this misconception

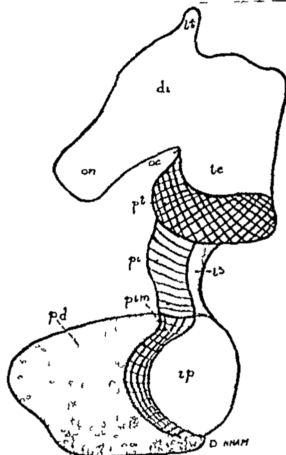


Fig 1 Reconstruction of hypophysial region in an adult female 61 years old Reconstruction illustrates the critical changes in the angulation of hypophysial axis This angulation now is approximately 90° with the floor of the third ventricle Specimen No 1184 di diencephalon ip infundibular process is infundibular stem le lateral eminence of tuber cinereum lt lamina terminalis oc optic chiasm on optic nerve pd pars distalis pi pars infundibularis pim pars intermedia pt pars tuberalis After Tilney with modification by Rasmussen

To avoid this dilemma the physiologist must know precisely what anatomical structures he has stimulated or destroyed experimentally How else can one correlate the experimental pathology with the resultant disordered physiology? For instance it is virtually impossible to puncture the preinfundibular area of the tuber cinereum without damaging and destroying portions of the adenohypophysial pars tuberalis The functional disorders, which are observed postopera

tively in such cases have been attributed almost universally to the hypothalamic damage alone Moreover observations on the pharmacological and physiological activity of extracts of the various divisions of the hypophysis cerebri presuppose an exact knowledge of the anatomical source of the crude material Failure to appreciate this viewpoint and to put it into practice cannot result in other than the misinterpretation of data and the improper anatomical localization of function A classical example of this type is to be found in the case of the pars infundibularis of the adenohypophysis It is a relatively large structure, which is closely adherent to and at some points merges with the pediculus infundibularis of the neurohypophysis It has been ignored for the most part in physiological and pharmacological experiments which have been aimed solely at the neurohypophysis Most pharmacological preparations of the so called posterior lobe' of the ox pig or sheep contain the anatomically conspicuous parenchyma of the pars infundibularis of the adenohypophysis but this factor has not been taken into account either at the bedside or in the laboratory

Allied to these problems and of equal importance is an understanding of the functional significance of the normal cytology of the hypophysis cerebri and of the cytological changes which characterize certain physiological states of the organism A useful clinical conception of the manner in which various hypophysial endocrinopathies are interrelated depends in large measure on information of this type

Finally a proper perspective of the morphological biological and clinical significance of the hypophysis must include some knowledge of its embryological development and its relation to the whole system of cerebral glands of which it is only a part albeit the most important in man

This chapter has been written with the foregoing considerations in mind and the incorporated clinical and experimental data have been discussed from this viewpoint whenever the opportunity has presented itself

Clinical Aspects of the Anatomy and Embryology of the Hypophysis Cerebri

General Appearance and Topography

The hypophysis cerebri is an ovoid reddish gray mass the diameters of which measure about 7 to 10 mm anteroposteriorly 10 to 15 mm transversely and 4 to 7 mm vertically As these measurements indicate the largest diameter of the gland lies in a frontal plane

The hypophysis occupies the fossa hypophyseos in the sella turcica of the sphenoid bone where it is roofed in by the diaphragma sellae The latter is fused

with the upper surface of the body of the gland The shape and differentiation of the hypophysial fossa varies considerably within certain limits The depth is the most variable of its three dimensions This circumstance has an important clinical bearing A growing hypophysial tumor can expand readily in all directions, when the fossa is shallow the anterior wall almost absent and the dorsum sellae poorly differentiated On the other hand, an expanding hypophysial tumor would be directed upward and forward when the anterior wall of the fossa is relatively low In such cases the dorsum sellae with its posterior clinoid processes is elongated and bent forward not infrequently More commonly, however, enlarging tumors of the hypophysis project backward and erode the dorsum sellae and its posterior clinoid processes Schaeffer[3] suggests that the course of direction of the infundibulum may be a factor in determining the direction of growth of a hypophysial tumor inasmuch as the majority of infundibula extend posteriorly and superiorly In this connection it is well to recall that the dorsum sellae is extremely variable in its differentiation and anatomy, and that the posterior clinoid processes may be absent congenitally Furthermore, deformation of the outlines of the sella with erosion of the posterior clinoids is by no means pathognomonic of a local lesion, because cerebellar tumors have been known to give an identical roentgen picture Hence the roentgen interpretation of alterations in the bony anatomy of the dorsum sellae must be made with caution

On either side of the sella turcica is the approximately longitudinal bony channel which contains the cavernous sinus These sinuses which drain the ophthalmic vein and its smaller tributaries also contain the post ganglionic nerves of the superior cervical sympathetic ganglia which reach them via the carotid plexus and four cranial nerves the third fourth sixth and ophthalmic division of the fifth The third cranial nerves pass forward through a lateral notch in the posterior clinoid processes and thus are particularly vulnerable to pressure from an enlarged hypophysis The relations of the hypophysis to the structures superior and anterior to it likewise are of special clinical importance Schaeffer[3] believes that the generally accepted views on this point are essentially inaccurate It is stated commonly that the chiasm lies in the optic groove of the sphenoid bone with the hypophysis and infundibulum posterior to the optic chiasm In a study of freshly exposed brains (Fig 2) Schaeffer found that this holds true for only 5 per cent of the cases (Fig 2 A) In 95 per cent of the cases the optic chiasm is located wholly or partly over the diaphragma sellae and the underlying hypophysis In 79 per cent of his preparations the hypophysis was found completely anterior and inferior to the chiasm and protruded somewhat laterally beyond the chiasm (Fig 2 C) In 12 per cent of the cases the chiasm itself lay markedly posterior to the optic groove while the body of the hypophysis was located directly beneath the chiasm (Fig B) When viewed from above por

tions of these hypophyses were visible anterior as well as posterior to the chiasm. In 4 per cent of Schaeffer's cases the entire mass of the hypophysis was located anterior to the chiasm with no visible protrusion laterally (Fig. 2 D). In such cases the entire optic chiasm is located behind the sellar diaphragm in such a fashion that it rests upon the dorsum sellae and partially projects behind it.

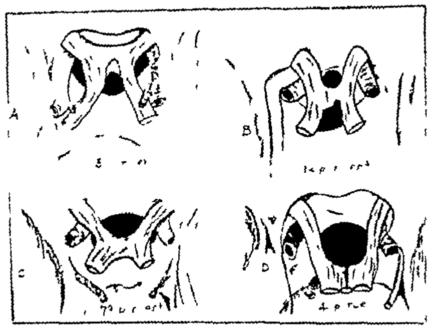


Fig. 2. Showing varieties of relations of the optic chiasm, internal carotid arteries and hypophysis. After J. Parsons Schaeffer.

A. The usually presented type but actually existing in only 5 per cent of the cases. The chiasm in the optic groove. B. The pituitary underlying the chiasm both anteriorly and posteriorly. The chiasm markedly posterior to the optic groove (12 per cent). C. The hypophysis completely anterior and inferior to the chiasm and protruding laterally beyond the chiasm. The most frequent finding (9 per cent). D. The entire mass of the hypophysis anterior to the chiasm with no lateral protrusion (4 per cent).

In order to reach its *postchiasmal position* the infundibular process must in most cases pass along the base of the chiasm anteroposteriorly in a saggital plane. Thus it practically comes into direct contact with the chiasm and occasionally even indents its inferior aspect. These anatomical relations indicate how readily an enlarging hypophysial gland can affect one or both aspects of the chiasm producing either a homonymous hemianopsia on the side contralateral to the pressure

or a bilateral hemianopsia depending on whether the lesion expands unilaterally or symmetrically These anatomical findings explain also how the disordered physical relations of an enlarged hypophysis could be transmitted along the course of the infundibulum and result in pressure and traction on the chiasm

The dorsum sellae and the posterior clinoid processes make up the posterior aspects of the hypophysis This wall is thin and poorly calcified as a general rule and occasionally it is found that an expanding hypophysial tumor which erodes the partition even exerts pressure on the posterior hypothalamic region and the crura cerebri The physical relations of the hypophysis and optic chiasm are such therefore that an expanding lesion in the sella turcica may account for a complex group of subjective and objective symptoms and signs which include visual field defects hemicrania and other types of headaches circulatory disorders within the ocular orbit and pressure effects on the crura cerebri with the attendant contralateral motor and sensory symptoms

Major Divisions and Subdivisions

The major divisions and subdivisions of the hypophysis cerebri, which are tabulated in Table I have been classified on a morphological basis from a functional viewpoint This classification has particular merit, moreover, because it conforms in all important respects with what is known of the embryology of the hypophysis In general the classification is that of Tilney[1] as adopted and modified by Rasmussen[4] The terminology which has been employed is in accord with the recommendations of the International Commission on Anatomical Nomenclature (see Fig 1)

TABLE I

DIVISIONS OF THE MAMMALIAN HYPOPHYSIS

Major Divisions		Subdivisions
Adenohypophysis	Lobus glandulari	1 Pars distalis
		Pars intermedia
		3 Pars infundibularis
		4 Pars tuberalis
Neurohypophysis	Lobus nervosus	Processus infundibuli
	Infundibulum	1 Pediculus infundibularis (stem)
		2 Bulbus infundibularis (bulb)
		3 Labrum infundibularis (rim) or median eminence of the tuber cinereum

The adenohypophysis is distinguished from the neurohypophysis primarily on the basis of their embryological origins The adenohypophysis which is derived from the somatic ectoderm consists of the pars distalis pars intermedia,

pars infundibularis and pars tuberalis The structural pattern of the adenohypophysis as a whole and the anatomical interrelations of its four constituent parts are determined by their origin and subsequent developmental growth It will be recalled that a marked evagination Rathke s pouch, takes place from the roof of the mouth early in the embryological development of the hypophysis (Fig 3) The epithelium of the stomodeum and the floor of the diencephalon are in contact

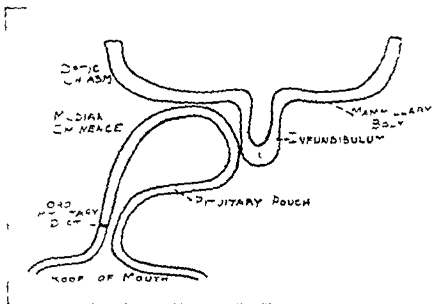
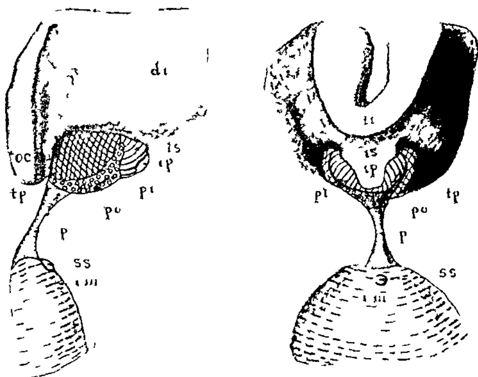


Fig 3 Sketch showing early relations of the pituitary pouch to the floor of the third ventricle particularly to the infundibulum After Tilney

and perhaps adherent to each other at this time Somewhat later there develops a protrusion downward from the floor of the ventricle This protrusion occupies a position which is immediately behind Rathke s pouch In the meantime a growth of mesenchymal tissue which invades the region between the floor of the brain and the roof of the mouth brings about a considerable separation of the oral cavity from the brain The connection between Rathke s pouch and the oral cavity lengthens gradually to form the long slender, oro hypophysial duct which eventually becomes solid and is known as the hypophysial stalk The ventral part of this stomodeal diverticulum becomes divided into two lateral lobes and a larger anterior portion in the 10 5 mm human embryo The anterior portion develops into the pars distalis of the adenohypophysis The pars tuberalis is derived from the bilateral extensions the tuberal processes of Rathke s pouch

which begin to fuse across the midline in the 45 mm embryo and eventually form a complete investment of the median eminence in the adult of the higher vertebrates

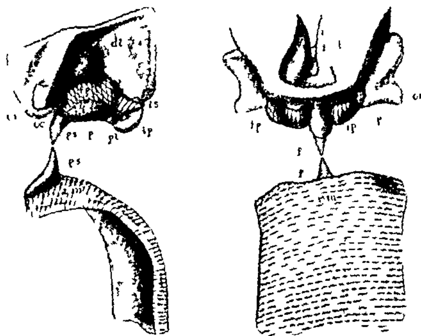
At about the same time two well defined changes occur in the dorsal or superior wall of Rathke s pouch, which is in contact with the neural protrusion from the



FIGS 4 AND 5 Left lateral and caudal views of reconstruction of hypophysial region in 16 mm human embryo Specimen No 1024 di diencephalon ip infundibular process is infundibular stem oc optic chiasm pi pars infundibularis po pituitary pouch ps pituitary stalk rm roof of mouth ss Seessel s pocket tp tuberal process After Tilney

entricle This juxtaneural epithelial region becomes thickened considerably and two caudal prolongations from it extend backward and almost surround the neural protrusion This thickened area together with its two caudal prolongations form the pars intermedia and pars infundibularis Tilney[1] prefers to regard this entire structure as the pars infundibularis On account of the long infundibular stem in the human hypophysis Rasmussen[4] has suggested, however, that the glandular parenchyma along the infundibular stem should be designated the

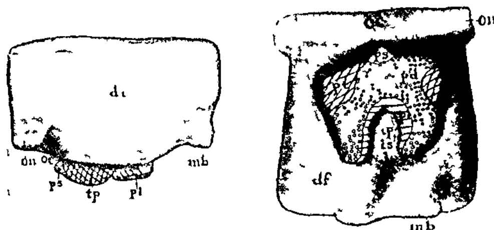
pars infundibularis, whereas the term pars intermedia should be reserved for glandular tissue which lies between the pars distalis and the processus infundibuli The extent to which the various portions of the adenohypophysis surround the infundibular stem in the adult is variable The pars infundibularis of the adenohypophysis may surround the infundibular stem completely as it emerges



Figs 6 and 7 Left lateral and caudal views of hypophysial region in 4 mm human embryo Specimen No 2010 di diencephalon ip infundibular process is infundibular stem oc optic chiasm on optic nerve pi pars infundibularis po pituitary pouch ps pituitary stalk rm roof of mouth tp tuberal process After Tilney

from the processus infundibuli The pars infundibularis and its continuation the pars tuberalis extend upward and become increasingly more posterior until they cover completely the posterior aspect of the infundibular bulb and the median eminence of the tuber cinereum The amount of glandular epithelium is variable and may become very scanty in the region of the upper portion of the infundibular stem and the tuber cinereum where there are numerous large vascular channels according to Wislocki[5,6,7]

As the anterior portion of Rathke's pouch grows larger, it is differentiated into an irregular highly vascularized network of cells which constitute the pars distalis of the adenohypophysis. The residual lumen of Rathke's pouch, which persists in most mammals and in the lower vertebrates, serves to separate the pars distalis from the pars intermedia and processus infundibuli. The pars intermedia is considered by some authorities[8] to be the most ancient part of the hypophysis. It



Figs. 8 and 9. Left lateral and basal views of reconstruction of hypophysial region in a 30 mm human embryo. Specimen No. 2040. df, diencephalic floor; di, diencephalon; i, infundibulum; ip, infundibular process; is, infundibular stem; mb, mammillary body; oc, optic chiasm; on, optic nerve; pd, pars distalis; pi, pars infundibularis; ps, pituitary stalk; pt, pars tuberalis; tp, tuberal process. After Tilney.

forms an investment of the processus infundibuli and usually is confined in its neural contact to the hypophysial surface of this process. The pars distalis is separated distinctly from the floor of the brain by a fairly thick layer of connective tissue as far back in its phylogenetic history as the cyclostomes. Its relation to the cerebrum thus is far less intimate than that of the pars infundibularis or the pars tuberalis. It is not surprising, therefore, to find that in the higher vertebrates, including reptiles, birds and mammals, the pars distalis becomes progressively more distant from the floor of the third ventricle. This glandular tissue of the pars distalis consists of two distinctly different regions, the cortex and medulla, each of which has distinguishing cytological characteristics which will be described in detail in another connection. The histological differences between the two portions of the pars distalis are distinct. The cortical zone takes a relatively light stain which discloses principally basophiles, among which are scattered numerous chromophobes, and its large acini are embedded in extensive interacinal cell

masses The medullary zone consists of smaller more compact acini its interacinal cell masses are more limited and its deeply staining cells are largely acidophilic'

The infundibular region towards which Rathke's pouch is attracted is by no means passive in the matter of biotaxis although as a general rule it is the somatic ectodermal anlage of the hypophysis which manifests the most pronounced growth *The intimate interrelations between the buccal and neural ectodermal* origins of the hypophysis and the dependence of each upon the other for normal growth are evidenced by failure of the somatic portion to develop if contact with



FIGS 10 AND 11 Lateral and caudal views of reconstruction of hypophysial region in a 5 months human fetus This stage shows the early effects produced by the lengthening of the infundibular stem and process The pars tuberalis is now completely exposed on the base of the brain as it invests the median eminence of the tuber cinereum Specimen 2022 df diencephalic floor di diencephalon ip infundibular process le lateral eminence mt mammillary body oc optic chiasm on optic nerve pd pars distalis pi pars infundibularis pr preoptic recess pt pars tuberalis e saccular eminence After Tilney

the floor of the brain is interfered with experimentally and by retardation in growth or abnormal development of the neurohypophysis if experimental ablation of the adenohypophysis is carried out early enough' In some species the infundibular region shows extremely active expansion and in all vertebrates it furnishes the central point of attraction towards which Rathke's pouch is directed and by which its growth is limited The infundibular region appears to have the most definite power of attraction in this phenomenon of biotaxis but the entire floor of the ventricle from the caudal fibers of the optic chiasm to the mammillary bodies is believed to exert a certain degree of attraction That the floor of the third ventricle other than the infundibular region exerts attraction for the glandular epithelium of Rathke's pouch is shown by the constant relations of the lateral processes or tuberal sprouts to the median eminence

The portion of the brain which contributes to the origin of the hypophysis

includes an area in the floor of the third ventricle extending from the caudal fibers of the optic chiasm to the mammillary bodies (Figs 10 and 11) The earliest parts derived from the neural ectoderm consist of the median eminence of the tuber cinereum and the infundibulum The median eminence represents a protuberance from the floor of the third ventricle which begins to take form immediately caudal to the optic chiasm and extends backward as far as the cephalic limits of the premammillary area The median eminence is characterized by a more pronounced degree of bulging in man and apes as compared with other mammals possibly because there is a greater descent of certain parts of the hypophysis into the deepened sella turcica of the primates The median eminence is flanked by the lateral eminences of the tuber cinereum In early embryonic stages the infundibulum is a funnel shaped process evaginating from the floor of the third ventricle just posterior to the area occupied by the median eminence The infundibulum is characterized embryologically by a ventral surface, which is in contact with the pouch destined to become the adenohypophysis and a dorsal surface which gives rise to a structure known as the saccus vasculosus[1] The relative position of the ventral and dorsal surfaces of the infundibulum which varies from species to species determines the regional topography of the fully developed neurohypophysis The saccus vasculosus has the characteristic histological architecture of a secreting glandular tissue in all species This has been determined by the structure of the epithelial cells as well as by the vascularity of this region Moreover phylogenetic studies particularly in reptiles birds and certain mammals e g the cat indicate that the saccus vasculosus is an integral part of the infundibulum and consequently of the neurohypophysis[1] This may be of considerable physiological significance Accepting Tilney's embryological observations at face value they imply that the so-called "posterior lobe" or processus infundibuli contains glandular inclusions derived from the saccus vasculosus It might be offered as a guarded suggestion that the nests of epithelial cells which occur as isolated clusters scattered throughout the dorsal portion of the processus infundibuli of the dog represent glandular inclusions derived from the saccus vasculosus

The infundibulum is a tapering extension from the ventral surface of the median eminence and contains a central cavity which is continuous with the third ventricle Its cavity is retained in the cat but disappears in man The infundibulum projects backward and downward from the caudal extremity of the median eminence in most mammals below the primates but in man the line of its projection is directly downward because of the descent of the hypophysis into the deepened sella turcica The infundibular structure consists of the bulb which marks its attachment to the floor of the third ventricle and the stem which connects the bulb with the infundibular process The latter is more commonly

known as the posterior lobe In man the infundibular stem is a solid stalk of considerable length which passes through an opening in the diaphragma sellae to terminate in the dependent part of the hypophysis known as the processus infundibuli

The four neural structures which have just been described are known as the labrum infundibularis or median eminence of the tuber cinereum the bulbus infundibularis or infundibular bulb the pediculus infundibularis or infundibular stem and the processus infundibuli or lobus nervosu They constitute the neurohypophysis and mu t be considered as a functional unit from a physiological and clinical viewpoint They contain at lea t two nerve fiber systems the supra-opticohypothalamic and tubero-hypothalamic tracts which extend from the hypothalamus through the tem and end in the processus infundibuli They will be described in detail in Part V and in the chapter on the hypothalamus

Because of the embryological and anatomical data which have been presented above it seems clear that the terms anterior lobe and posterior lobe are inadequate either from a physiological or a morphological viewpoint As a corollary one must conclude furthermore that the interests of the clinician and the pathologist are erved best by the adoption of the nomenclature and conception fostered by Tilney and others of his way of thinking

The Craniopharyngeal Duct and Canal

Inlage and Incidence — In order to emphasize the functional as well as the morphological aspects of the foregoing cla ification certain special phases of the developmental history of the hypophysis cerebri are recorded herewith Such an approach serves to clarify the clinical significance of certain embryological rests in the hypophysial area The relation of these vestigial remnants to the origin of tumors which are peculiar to this region is an important part of this problem

Rathke s original conclusion that the hypophysis cerebri has a two-fold anlage is accepted almost universally now Most investigators including Tilney[1] Kolliker Dohrn[4] Froriep[13] Scott Balfour Emery[3] and Mirot[4] have upheld Rathke s belief that the hypophy is arises from two specialized sources of ectoderm the somatic ectoderm in or about the region of the roof of the mouth and the neural ectoderm in the floor of the third ventricle This interpretation of the available embryological data has been challenged by Hoffman[79] Kupffer[1] Valenti Prather Bruni and Balfour and Parker on the ba is of their studies of bony fish amphibia and reptiles Their observations have disclosed what they take to be an entodermal participation in the formation of the hypophy is In view of this evidence one mu t conclude that the entoderm does participate in the formation of the gland in some lower vertebrates but there is no reason as y t to

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marks the position of the so called craniopharyngeal canal Tilney[1] could not be certain whether this canal was patent but concluded that it did not contain remnants of the hypophysial stalk in any event

There are certain clinical aspects to the so called craniopharyngeal canal which are pertinent to the discussion This structure was named in 1868 by Landzert [8] who found a complete canal passing through the body of the sphenoid bone in 10 per cent of newborn children and Le Double [9] in 1903 observed the same incidence under similar circumstances In view of more recent studies Cave[30] believes that they were confusing this canal with the relatively common vascular foramina of the sphenoidal body Tilney[1] states that it occurs in less than 0 5 per cent of presumably normal crania of all ages and Cave[3] concurs with an incidence of 0 2 per cent based on a study of adult human skulls Greig [1] has observed it in 40 per cent of anthropoid apes and has encountered it relatively frequently in other animals Tilney believes that it should be called the orocranial canal inasmuch as its ventral end originates primarily in relation with the roof of the mouth and only secondarily comes to occupy a position in the pharynx where it is situated 5 5 mm posterior to the nasal septum Reference to it as the craniopharyngeal canal implies erroneously that the hypophysis is derived from the pharynx Evidence of its vestigial remains may be disclosed occasionally by an opening in the floor of the sella turcica [9] Cave [0] recorded such a case in a 38 year old male The mouth of the craniopharyngeal or orocranial canal was a circular hole in the floor of the sella turcica 3 5 mm in diameter which could be entered by a probe for a distance of 16 mm downward and forward through the median septum of the sphenoidal sinus to a vomerine termination in the nasal septum Cases have been reported in which the canal is complete and contains a prolongation of dura which merges with the periosteum covering the undersurface of the sphenoid bone Other instances have been observed however in which the canal is incomplete contains a dural cul de sac with or without hypophysial tissue and terminates in the body of the sphenoid or in the posterior part of the nasal septum An example of this type where an incomplete canal was filled by a solid epithelial plug was observed in a 4 year old child by Suchannek[8] When the canal presents an inferior opening Cave states[3] that the aperture is located usually about 1 5 mm behind the postero superior angle of the vomer Frazier [9] points out similarly that the ventral extremity of the craniopharyngeal canal ends in or near the vomer bone Haberfeld [4] reviewed 73 cases of persistent craniopharyngeal or orocranial canal and concluded that the canal is more likely to be present if other malformations are found According to Goldzieher[25] the canal can be recognized on lateral roentgenograms of the skull

Clinical Significance of Vestigial Remnants — The Craniopharyngioma — Although divergent views are held concerning the possible fate of certain of the

implicate the entoderm in the embryological development of the hypophysis of the primates Tilney's summary[1] of the evidence indicates that entodermal cells of the foregut notochord or premandibulbar somites apparently do not enter into the formation of this organ these structures are contiguous to, but probably not continuous with, the germ layers which participate in the formation of the gland

There is some discussion over the nature of the forces that take part in the early approximation of the somatic and neural ectodermal tissues which contribute to the formation of the hypophysis Gilbert states, contrary to general belief, that the hypophysis is not formed from evaginations, which arise from their respective anlage and that the latter do not approach each other through biotaxis[6, 7] Her observations indicate that the hypophysis develops at a point where the two ectodermal anlage are adherent long before either of the hypophysial diverticuli is recognizable and the manner in which the head region of the embryo develops, viz, the mechanical forces induced by the ventral bending of the forebrain apparently determine the formation and shape of Rathke's pouch More general acceptance has been accorded the theory, however which proposes that tubular diverticuli in the form of closed sacs grow out from the ectodermal anlage Having been attracted definitely to each other by virtue of biotaxis they meet to form the hypophysis According to this conception Rathke's pouch grows out dorsally from the ectoderm of the primitive buccal cavity its precise point of origin being subject to some variations in the various phyla (see Fig 3) Rathke's pouch communicates at first with the buccal cavity through a wide connection in the roof of the mouth Later this connection becomes elongated to form a slender tubular structure known as the *craniopharyngeal duct* The latter is a misnomer according to Tilney[1] because the duct takes origin from the roof of the mouth and not from the pharynx Tilney has suggested a more appropriate name the *oropituitary duct* In keeping with the nomenclature adopted for this chapter one might refer to it as the *orohypophysial duct* Subsequently, early in its development the orohypophysial duct becomes a solid structure the hypophysial stalk which extends between the roof of the mouth and Rathke's pouch Coincident with these changes the mesenchyme invades extensively the region between the floor of the brain and the roof of the mouth The mesenchymal foundations of the sphenoid bone are formed in this manner and the hypophysial stalk, which is surrounded by rapidly growing sphenoidal mesenchyme comes to occupy the so called *craniopharyngeal canal* The hypophysial stalk, which develops from the extremely transitory orohypophysial duct becomes attenuated and disappears in turn except for a small remnant which remains attached to the roof of the mouth while another remnant can be identified at the cephalic extremity of the hypophysis According to Tilney[1] the sphenoidal anlage in the 30 mm human embryo is distinctly cartilaginous and contains a small circular area near its center, which

The tumors are of two types in general viz cystic or solid The cysts may be smooth, thin walled and unilocular or multilocular The solid tumor usually is firm and lobulated Mixed varieties of tumors are not infrequent There are solid squamous cell tumors containing intracystic papillomatous structures and others in which degeneration and cyst formation occur because of a blood supply which becomes inadequate as the tumor increases in size In such cases secondary calcification and ossification of the wall may serve as an important roentgenological diagnostic sign At operation such cystic tumors frequently are found to be filled with thick grumous fluid rich in cholesterol crystals of cholesterol may lie free in the fluid and are to be found also in the fibrous tissue wall The latter have been confused with meningeal cholesteatomata The solid tumors are of two kinds ordinarily, i e the epidermoid cell carcinoma of the squamous type and the basal cell carcinoma of the adamantinoma variety The epidermoid cells are of the usual structure with typical intercellular bridges and keratinization and the tumor tends to metastasize The basal cell type which usually invades adjacent structures but does not metastasize is characterized by a centrally placed enamel syncytium, within which are epidermoid pearls the horn pearl formation and a peripheral columnar enamel epithelium [8] Teratomas are rare in the vicinity of the sella turcica[4]

The symptoms and signs produced by the so-called craniopharyngiomas will be discussed in detail in relation to the pathogenesis of dwarfism For the present it is sufficient to state that they may elicit obesity hypersomnolence and polyuria by virtue of pressure upon or invasion of the hypothalamic region Pressure atrophy of the adenohypophysis in children results among other things in retarded somatic and gonadal growth loss of body hair and hypometabolism Failing libido impotence and amenorrhea develop in postpuberal individuals under similar circumstances It is pertinent to note in this connection that the hypothalamus may be involved in the production of certain symptoms which have been ascribed heretofore to adenohypophysial dysfunction alone The basis for this suggestion is being discussed at some length elsewhere in the chapter on the hypothalamus

Pharyngeal Hypophysis — The pharyngeal hypophysis is named incorrectly from an embryological viewpoint because the hypophysial structures of which it is a vestigial remnant take origin from the roof of the mouth and not from the pharynx According to Cave [0] the so-called pharyngeal hypophysis was observed originally by Killian in 1888 It was studied subsequently by Erdheim[35] Haberfeld [1] Cristeller[42] Gautier [2] Pende[4] and Melchionna and Moore[45] It is said to be present almost constantly in humans if carefully searched for Melchionna and Moore[45] observed it in 51 of the 54 cases they studied They found the pharyngeal hypophysis in the midline beneath or near the vomerosphenoidal

residual structures of the early buccal anlage, there is general agreement on the thesis that the craniopharyngioma type of tumor takes origin from these vestigial structures. According to Tilney[1] there is no acceptable proof that any part of the orohypophysial duct is carried over into the adult state of man. It should be recalled, however, that one remnant of the orohypophysial duct remains attached to the roof of the mouth, presumably becoming the so-called *pharyngeal hypophysis*, whereas another remnant has been observed at the cephalic extremity of the hypophysis. Embryologically the latter becomes associated intimately with the developing pars tuberalis of the adenohypophysis. This may be significant inasmuch as Atwell believes that tumors in this general area take origin from rests in the pars tuberalis. Atwell's conception appeals to Tilney[1] because it explains satisfactorily the presence in this region of tumors of the adamantinoma structure. The early intimate relation of the hypophysial plate to the dental ridge accounts for the inclusion of dental elements into the anlage of the pars tuberalis. Tilney objects to Erdheim's postulation[3] that tumors of the so-called craniopharyngioma type are derived from embryological rests along the course of the orohypophysial duct. The importance of Erdheim's observations must be recognized, even though Tilney may be correct concerning the complete disappearance of the orohypophysial duct early in the development of the embryo. Erdheim was the first to ascribe the origin of the craniopharyngioma type of tumor to the anlage of the orohypophysial duct. It should be recalled in this connection that the pars tuberalis is derived embryologically from paired structures which bud from the orohypophysial duct. From an embryological viewpoint, therefore, Atwell's theory is not far removed from that of Erdheim.

As might be expected, the so-called craniopharyngioma usually is suprasellar due to its probable origin from embryonal squamous cell rests in the pars tuberalis of the adenohypophysis. Occasionally, however, the tumor may develop within the sella turcica itself, a finding which is compatible also with the embryological characteristics of this region. The tumor may appear at any period of life but is especially common under fifteen years of age. It attains a much larger size ordinarily than the average hypophysial adenoma. Because of its usual suprasellar position it does not balloon out the sella turcica like the latter tumor but flattens it from above downward. As a result of this pressure it destroys the diaphragma sellae and erodes the dorsum sellae at the same time that it produces pressure atrophy of the hypophysis cerebri. The atrophy of this gland may be so complete that it is recognizable only microscopically. These tumors also grow upward and encroach either by pressure or invasion upon the tuber cinereum and the wall of the third ventricle. In some instances the cavity of the third ventricle itself is invaded and the circulation of the cerebrospinal fluid is interfered with so that marked hydrocephalus of the lateral ventricles develop.

Weight of the Constituent Parts in Relation to Race Sex Age Body Measurements and Pregnancy

The human hypophysis varies greatly in weight under conditions which are well recognized for the most part The factors with which these significant variations have been correlated are race, sex, body height and weight, age and physiological states such as pregnancy

The average weight of the hypophysis of the negro is greater than that of white people[4] The female hypophysis is heavier on the average than that of the male in all races which have been studied[4] Rasmussen s studies[46 7] of 111 adult men with an average age of 45 years and 93 non pregnant females with an average age of 41 years disclosed that the hypophyses of the former ranged in weight from 358 to 788 mgm , average 526 mgm while those of the latter ranged in weight from 448 to 971 mgm , average 618 mgm The pars distalis which is larger in the female than in the male accounts for the difference in size The processus infundibuli and pars intermedia on the other hand are significantly larger in the male Since the body weight of the female is less than that of the male ordinarily the proportional size of the female hypophysis exceeds the male gland even more than does its actual size Rasmussen has demonstrated also that there is a sex difference in the tendency for the outgrowth of tubular glands from the pars intermedia into the processus infundibuli inasmuch as such glands are noted more commonly in females than in males[48] There is a statistically significant positive correlation between body length or height and the weight of the hypophysis[4 49 50] The existence of a correlation between body weight and hypophysial weight has not yet been established with certainty[50 51 52] There is no correlation between the percentage of acidophilic cells in the hypophysis and stature although these cells are believed to be the source of the growth hormone[4]

The pars distalis of the male hypophysis decreases significantly in weight after middle age whereas the processus infundibuli and the epithelial elements of the pars intermedia tend to increase with age[4] In the female age changes are not reflected clearly in the weight of the whole gland a they are in the male Pars distalis retains its weight better than in males and the processus infundibuli and pars intermedia increa e distinctly The growth of pars intermedia with age is due to an increase in basophilic cells which tend to invade the processus infundibuli[4]

The hypophysis becomes markedly enlarged during pregnancy[4 53] The amount of enlargement depends on the duration of pregnancy the length of time intervening between parturition and death and apparently also on the number of previous pregnancies Rasmussen s data indicate that the average weight of hypophyses of 8 primipara is 820 mgm whereas the corresponding figure for a

articulation deep in the mucosa or in the periosteum It occurs most frequently in the shape of a single flattened spheroid which is well circumscribed and en capsulated In a few instances irregular cords or islands of cells extend into the surrounding tissue

The largest pharyngeal hypophysis noted by Melchionna and Moore[45] was in a 15 year old girl and it measured 6 67 mm in length, 1 15 mm in width and 0 55 mm in depth The smallest gland they encountered was in a newborn infant and its dimensions were 0 22 mm in length, 0 21 mm in width and 0 10 mm in depth In a study of 51 cases Haberfeld[41] found that most of the growth of this gland occurred in the fetus during the first few months of life and that there was little or no enlargement thereafter This has been confirmed by Melchionna and Moore[45]

Studies of the histology of the pharyngeal hypophysis have disclosed essen tially two types of tissue viz undifferentiated epithelial cells and differentiated cells similar to those of the adenohypophysis Melchionna and Moore[45] have reported that the undifferentiated epithelium was present in 32 of their 51 cases It is usually of the transitional type but in rare instances there may be definite intercellular bridges Keratinization and keratin granules do not occur The undifferentiated cells are arranged in small nests with an indefinite basal layer Cyst formation within the transitional epithelium occurs infrequently Not un commonly there are glandular acini which are lined by columnar or cuboidal cells and associated with nests of transitional epithelium The acini contain a homoge neous acidophilic substance The differentiated tissue has the same histological appearance as that of the adenohypophysis but there are conspicuous quanti tative differences between them The pharyngeal hypophysis shows a striking deficiency of basophilic and acidophilic cells They constitute less than 1 per cent of all cells In 25 per cent of the cases reported by Melchionna and Moore there were no chromophilic cells and in 35 per cent either the acidophilic or the basophilic cells were absent Fuchsinophilic colloid was associated frequently with the chromophilic cells and was conspicuous in 11 of their cases

The interstitial tissue and vascular supply of the pharyngeal hypophysis is essentially the same as that of the adenohypophysis There are numerous myelinated nerves and large vascular sinusoids in the tissue surrounding the pharyngeal hypophysis in most cases

Melchionna and Moore[45] have concluded that the pharyngeal hypophysis is not physiologically active in normal states of growth and metabolism Although the pharyngeal hypophysis does not appear to develop compensatory changes or hypertrophy when adenohypophysial function is disordered, there are some histological data which suggest that it is functionally active under certain circum stances[45]

and is far less intense than the corresponding physiological state in the female It should be recalled in this connection that the increased percentage of basophiles in the hypophysis of the menopausal woman occurs coincidentally with the increased urinary excretion of follicle stimulating hormone FSH This evidence of physiological hyperactivity of the pars distalis which is encountered commonly in the climacteric female occurs relatively infrequently in the middle aged male

The correlation between body length and the weight of the hypophysis also appears to have clinical significance and will be considered more fully in connection with the cytology of the pars distalis The increase in weight of the hypophysis during pregnancy may be of especial clinical importance because it probably contributes to the development of certain pathological states such as acromegaly hyperthyroidism and diabetes mellitus which complicates pregnancy sometimes This matter will be discussed further in connection with the cytophysiology of the adenohypophysis

Meningeal Relations

The meningeal relations of the hypophysis cerebri (Fig 12) are of clinical importance for at least two reasons In the first place the manner in which the meninges develop embryologically determines the mode and distribution of vascularization of the constituent parts of the hypophysis Consequently these data may have a specific bearing on the problem concerned with pathways of hormonal secretion The latter will be considered in connection with a description of the nerve and blood supply of the hypophysis Secondly the anatomical relations of the diaphragma sellae and the hypophysis throw considerable light on the direction in which a growing sellar tumor may expand

As a result of the studies of Schwartz and of Wislocki [8] it has been determined that neither the subarachnoid space nor the subdural space surround the hypophysis within the sella turcica The capsule of the body of the hypophysis, the dura lining the ella turcica and the periosteum covering the sph roid bone are intimately fused (Fig 12) This anomaly occurs because the dura becomes attached firmly to the body of the hypophysis before the meninges in this region are differentiated completely thus precluding the formation of a subarachnoid or subdural space within the sella turcica Early in its embryological development the hypophysis having been completely cut off from its oral origin comes to lie in a field of mesenchyme before the latter has undergone differentiation into meninges Subsequently the mesenchyme surrounding the body of the hypophysis gives rise to a lamina of dura which encloses the gland firmly and becomes attached to a portion of its upper surface leading to the formation of the diaphragma sellae

group of 46 multipara with a similar duration of pregnancy is 954 mgm If one limits such observations to multipara, who reached about full term and died within one week after parturition instead of up to two weeks as in the preceding groups the average hypophysial weight in 22 cases is 1,070 mgm A review of Rasmussen s data shows furthermore, that the difference in weight between the hypophyses of non pregnant and pregnant women is due entirely to an increase in the size of the pars distalis and amounts to well over 100 mgm Pars intermedia is smaller, if anything in the group of pregnant women

The physiological and consequently the clinical, significance of these variabilities in hypophysial weight have not been established with certainty There are too little data on differences which apply to racial groups, and this would seem to be a lucrative field of investigation for the geneticist and for those interested in the constitutional aspects of endocrine physiology So far as the physiology of the hypophysis is concerned the outstanding difference between the male and female gland is in its gonadotropic activities The occurrence of ovulation in connection with the menstrual rhythm and the phenomena of pregnancy parturition and lactation obviously require a highly complex physiological integration with other endocrine glands and body tissues Furthermore these unique female functions as compared with the physiology of the male sex hormone, call for a far greater precision in the homeostatic mechanisms which regulate organ and tissue metabolism That the acidophilic cells of the hypophysis play n important role in these anatomical and physiological differences is suggested by the fact that they are significantly more numerous in females than in males Thi conception is in accord with the data of Friedgood and Dawson [4, 55, 56], who note a striking increase in the number of carmine cells during ovulation, parturition and lactation in rabbits and cats The carmine cell represents a functional variety of the ordinary acidophile

As noted above, the weight of the hypophysis as a whole and of the pars distalis in particular changes little after middle age in the female whereas it decreases significantly in the male This regression in hypophysial weight which occurs after physiological castration in the climacteric state is associated with a decrease in the percentage of acidophiles, an increase in the population of chromophobes and no significant numerical changes in the basophiles[4] On the other hand the relatively unchanged hypophysial weight in menopausal women is associated with a perceptible increase in the percentage of basophiles[4], while the percentages of acidophiles and chromophobes shift as in the male These findings may supply an anatomical and cytological basis to account for the clinical differences between the menopausal state of the male and female The regression in weight of the pars distalis and the lack of increase in the percentage of basophiles may explain why the male climacteric syndrome occurs much more infrequently

and is far less intense than the corresponding physiological state in the female. It should be recalled in this connection that the increased percentage of basophiles in the hypophysis of the menopausal woman occurs coincidentally with the increased urinary excretion of follicle stimulating hormone FSH. This evidence of physiological hyperactivity of the pars distalis which is encountered commonly in the climacteric female occurs relatively infrequently in the middle aged male.

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As a result of the studies of Schwartz and of Wislocki[8] it has been determined that neither the subarachnoid space nor the subdural space surround the hypophysis within the sella turcica. The capsule of the body of the hypophysis, the dura lining the sella turcica and the periosteum covering the sphenoid bone are intimately fused (Fig 12). This anomaly occurs because the dura becomes attached firmly to the body of the hypophysis before the meninges in this region are differentiated completely, thus precluding the formation of a subarachnoid or subdural space within the sella turcica. Early in its embryological development the hypophysis, having been completely cut off from its oral origin, comes to lie in a field of mesenchyme before the latter has undergone differentiation into meninges. Subsequently the mesenchyme surrounding the body of the hypophysis gives rise to a lamina of dura which encloses the gland firmly and becomes attached to a portion of its upper surface leading to the formation of the diaphragma sellae.

The meningeal relations of the processus infundibuli likewise are noteworthy A mass of mesenchyme intervenes between the developing adenohypophysis and the base of the diencephalon to which it becomes attached by a slight condensation of cells forming pia mater The connective tissue stroma of the buccal hypophysis develops from this pial hypophysial mesenchyme by a gradual process

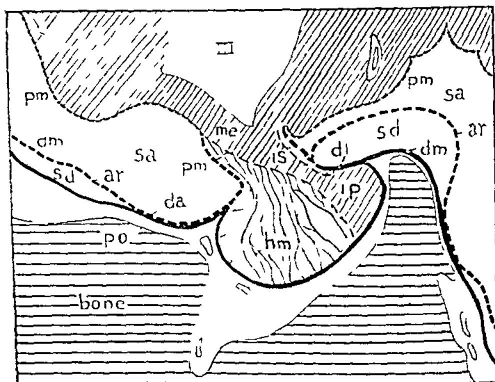


FIG 12 Diagram of the meninges in the hypophysial region of a human fetus of 160 mm Solid line dura mater (dm) Heavy interrupted line arachnoid membrane (ar) Light interrupted line pia mater (pm) It will be noted that the subarachnoid space (sa) forms a collar around the infundibular stalk (is) The pia arachnoid does not penetrate the sella instead the body of the pituitary is surrounded by dura (dm) which is fused with the free pole of the infundibular process (ip) and forms the sellar diaphragm (di) upon the upper surface of the body of the pituitary

At the margin of the pars tuberalis which extends forward beneath the median eminence (me) of the tuber cinereum pia mater (pm) and arachnoid (ar) meet In consequence the free surface of the pars tuberalis facing the subarachnoid space is covered by arachnoid

The pia mater (pm) is indicated by an interrupted line between the neurohypophysis and the buccal hypophysis Furthermore this lamina of pia is connected with a series of lines representing connective tissue stroma which subdivides the epithelial hypophysis The origin of the stroma (hm) from the pial hypophysial mesenchyma of earlier stages is indicated diagrammatically in this manner After Wislocki

of interdigitation of mesenchymal cells and hypophysial parenchyma. The delicate condensation of cells which occurs on the surface of the diencephalon surrounds the entire neurohypophysis at first. Soon however the infundibular process pushes its way into the mesenchyme of the developing fossa in the sella turcica. As a result it loses any distinctive pial covering which it may have had and fuses with the dura within the sella. The free pole of the infundibular process thus becomes attached to the dura. When completely differentiated the subarachnoid space and the subdural space form a cistern which encloses the infundibular stem in the form of a collar. The sellar diaphragm which is fused with the upper surface of the body of the hypophysis intervenes between the subarachnoid and subdural spaces on the one hand and the sella turcica on the other.

The diaphragma sellae is a small more or less oval layer of connective tissue which roofs the hypophysial fossa in the horizontal plane. The foramen of the diaphragma sellae is an extremely variable opening through which the infundibular stem emerges from the sella turcica. The diaphragm is composed of fibro elastic tissue which varies from a very dense strong structure with a very small foramen to one which is frail largely absent and pierced by a relatively large infundibular foramen. In some cases the greater portion of the diaphragm may be more or less fenestrated and of delicate structure.

The anatomy of the diaphragma sellae may influence the direction of growth of a hypophysial tumor at times. A tumor can expand readily toward the optic chiasm when the diaphragm is essentially absent or poorly developed. On the other hand such tumors are more likely to expand in the direction of the sphenoidal sinuses if the latter are highly pneumatized and the diaphragm is exceptionally tough and complete. A large opening in the diaphragm often delays recognition of an intrasellar tumor since it obviates the early headaches associated with expanding intrasellar neoplasms. In such cases decompression occurs through the enlarged infundibular foramen.

Blood Vessels and Lymphatics

Arteries and Veins in the Mature Human Hypophysis. — The vascular supply of the hypophysis cerebri (Fig. 13) has been studied minutely by Wislocki and others[47, 48, 49]. It has been determined that the blood supply of the human hypophysis coincides with that of the rhesus monkey[51]. The main arterial channels consist of the superior and inferior hypophysial arteries[47]. The superior hypophysial arteries are derived from the internal carotids and the posterior communicating arteries. These vessels are distributed to the infundibulum and the adenohypophysis. The twigs entering the adenohypophysis break up into sinus

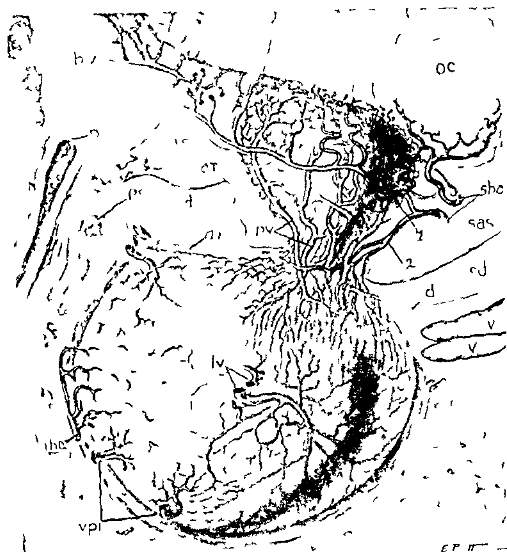


FIG 13 Schematic drawing of the hypophysis of the adult rhesus monkey ar arachnoid membrane ba basilar artery bv basilar veins d dura di sellar diaphragm iha inferior hypophysial artery lv lateral hypophysial veins oc optic chiasm pc posterior clinoid process pv portal venules sas subarachnoid space sd subdural space sha superior hypophysial arteries (1 branches to hypophysial stalk 2 branches to anterior lobe) v dural vein vpi veins of infundibular process After Wislocki

oids Those vessels which supply the infundibulum enter a plexus of capillaries of sinusoidal character which surrounds and penetrates it The inferior hypophysial arteries arise from the internal carotids in the cavernous sinuses and

supply the processus infundibuli or lobus nervosus by entering its free pole and breaking up into a capillary bed

In addition to the systemic veins which will be described the adult human hypophysis is supplied with portal venules[5,7,5,9,6] These lie beneath the branches of the superior hypophysial arteries for the most part They arise by a confluence of small vessels on the surface of the infundibular stem and are derived from two sources first from a plexus of capillaries of wide caliber on the surface of the infundibular stem and secondly from a number of arborizing tufts of wide capillary plexuses which subdivide the interior of the infundibular stem Both the deep and the superficial plexuses of the stem drain into numerous portal *venules which eventually penetrate the parenchyma of the pars distalis and end* in its sinusoids Thus the sinusoids of the pars distalis resemble those of the liver in that they are supplied by arterial and venous afferent vessels

According to Wislocki and King [7] the portal venules are not continuous with the vascular supply of the hypothalamus except in so far as the plexiform capillary bed of the infundibular stem connects through the interior of the stem with the capillaries of the general brain net of the hypothalamic region (Fig 14) The vascular transition between stem and hypothalamus is rather abrupt and very few vessels other than these capillary connections bridge the gap Wislocki believes that the direction of blood flow is from hypothalamus to infundibular stem and not vice versa as was suggested by Popa and Fielding [9,60] As quoted subsequently the latter have reported that the portal circulation drains the sinusoids of the pars distalis ascends the stalk and breaks up into a capillary network within the hypothalamic region

The systemic veins consist mainly of lateral hypophysial vessels on each side draining from the adenohypophysis into the cavernous or intercavernous sinuses and of veins which convey blood from the infundibular process into the cavernous sinuses Contrary to the observations of others Wislocki has not observed suprasellar systemic veins accompanying the superior hypophysial arteries

Embryological Aspects of Hypophysial Vascularization —The unique features of the angio architecture of the hypophysis are a result of the way in which *the gland is vascularized embryologically According to Wislocki[9,7] the brain* as a whole is ensheathed in a delicate plexus of pial vessels to which arteries and veins can be traced in the 18mm and 21 mm human embryo This pial plexus covers also the base of the diencephalon including the infundibulum and vascularizes the lamina of the undifferentiated mesenchyme which occupies the area between the base of the brain and the epithelial portion of the hypophysis Wislocki has named this network of capillaries the *pial hypophysial plexus* The latter is nourished by arteriolar twigs arising from the internal carotids or the posterior communicating arteries of the circle of Willis These arterioles are des

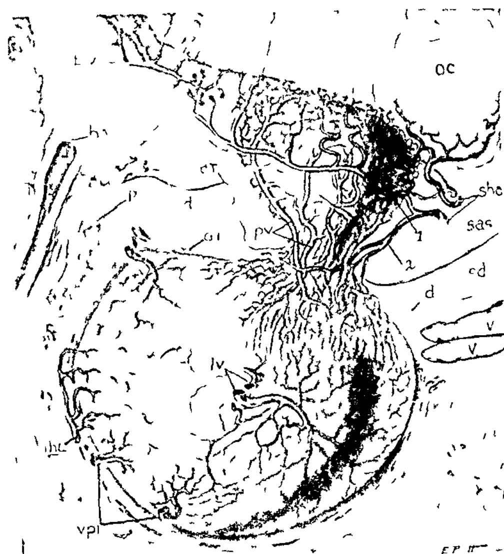


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tined to become the superior hypophysial arteries supplying the pars distalis in addition to sending branches to the pial plexus which surrounds the infundibular stem and vascularizes the latter the tuber cinereum, the pars infundibularis and the pars tuberalis

Beginning with the 25 mm stage of the human embryo the pial hypophysial mesenchyme which develops between the embryonic adenohypophysis and the floor of the third ventricle gives rise to the stroma of the adenohypophysis by invading its parenchyma along well-defined vascular grooves[1] The adenohypophysial parenchyma becomes subdivided finely by this stroma which being extremely vascular, conveys with itself a rich plexus of capillaries arterioles and venules This plexus of vessels soon establishes multiple secondary connections with the venous or cavernous plexuses which occur in the developing dura of the sellar region The pial hypophysial plexus gives rise moreover to the typical sinusoids of the adenohypophysis The secondary connections which are established between the adenohypophysial sinusoids and the cavernous plexuses become the main systemic venous channels of the pars distalis The embryonic adenohypophysis thus acquires a dual venous drainage viz from above through the primary pial venules of the pial hypophysial plexus and from below through the multiple secondary connections which are established with the developing cavernous plexuses The latter are in the mesenchymal region which is to become the sella turcica The primary venous channels from above are destined to atrophy leaving these secondary venous connections the lateral hypophysial veins since the principle efferent veins do not accompany the superior hypophysial arteries in the adult

Because of the attachment of the dura mater to the distal end of the neurohypophysis the processus infundibuli receives its vascular supply from the dura not from the pia mater The inferior hypophysial arteries which are of dural origin penetrate the infundibular process from each side near the midline and break up into its capillary bed The inferior hypophysial arteries arise from the internal carotid arteries in the cavernous plexus The rich vascular bed of the infundibular process drains into a number of collecting veins which emerge from the surface of the gland at various points and then empty into the adjacent cavernous and intercavernous sinuses The arteries and veins of the processus infundibuli being dural in origin, are independent of the vascular supply which reaches the infundibular stem and adenohypophysis from the pial hypophysial plexus

No one knows for certain how the portal venules arise Wislocki has an interesting suggestion in this connection[6,7] He points out that in the adult few if any pial venules connect the infundibulum with the basilar or other pial veins Consequently, the fetal pial venules which drain the embryonic infundibulum and pars distalis must undergo almost complete obliteration It is his belief that



Fig 14 The dissected hypophysial stalk and hypothalamus split in the mid sagittal plane revealing the vascular plexuses within the hypophysial stalk The transitional vessels between the median eminence (me) of the hypophysial stalk and the hypothalamus are shown The largest of these (v) is a vessel of undetermined character A minute arteriole (art) traversing the boundary of the stalk and hypothalamus is also visible An hypothalamic vein (ev) is seen it passes to the surface and drains into a branch (bbv) of one of the basilar veins It is clear from study of the blood vessels in the transition zone between hypophysial stalk and brain proper shown in this figure that there are no significant vascular links between the hypophysis and the more important nuclear centers of the hypothalamus for example the paraventricular nucleus (pvn) After Wislocki

to the infundibular stem from whence the circulation enters the sinusoids of the pars distalis

The angio architecture of this region may be a clue likewise to the mechanism by means of which the adenohypophysis is stimulated physiologically This is unknown at present although it is well recognized that the neurohypophysis is activated functionally by way of the supra optico hypophysial and tubero hypophysial nerve tracts As compared with the physiological importance of the adenohypophysis on the other hand there is a relative dearth of nerve fibers to *which one could attribute stimulation Humoral stimulation of the pars distalis* could be accomplished however through the portal circulation which undoubtedly collects the products of secretion of the areas it drains Because of the vascular connections *which are known to exist between the capillaries of the general* brain net of the hypothalamus and the infundibular stem it is possible moreover that secretions of the hypothalamic neuronal cells are carried to the pars distalis through these vascular channels

Nerve Supply

Introduction —The gonadotropic functions of the adenohypophysis have *been used almost exclusively to investigate its functional innervation principally* because they lend themselves to experimental study It is a matter of common knowledge that the gonadotropic activities of the adenohypophysis are influenced *considerably by the nervous system From a clinical viewpoint* it has been noted that fear anxiety or indeed any strong emotional experience can interrupt the regularity of the normal menstrual cycle for one or more periods In the laboratory it can be demonstrated that mechanical or electrical stimulation of the cervix uteri of the rat induces a prolonged period of diestrus known as pseudopregnancy presumably *because it initiates a neural stimulus which activates the adenohypophysis* The luteotropic hormone prolactin which is secreted in response to this stimulus thereupon prolongs the functional life of the last formed corpora lutea beyond *that encountered in the normal estrous cycle*

The Cervical Sympathetics —Connection of a Branch of Third Cervical Nerve with the Superior Cervical Sympathetic Ganglion —From an anatomical viewpoint it is reported that postganglionic fibers originating in the superior cervical sympathetic ganglia reach the adenohypophysis through the carotid plexus and end in contact with individual cells [3 6 8] In attempting to trace this pathway physiologically Friedgood[39] noted that a tiny strand of myelinated fibers connecting one of the branches of the cervical plexus third cervical nerve and the inferior pole *of the superior cervical sympathetic ganglion is involved in the* transmission of neural impulses from the cervix uteri to the adenohypophysis

the portal venules which connect the infundibulum with the pars distalis in the adult may represent the modified distal remnants of the pial venules which originally drained the pial hypophysial plexus. The concept advanced by Espinasse[5] is quite to the contrary and postulates that the portal venules are modified pial arteries which carry blood from the pars distalis to the infundibulum and hypothalamus. Wislocki disagrees vigorously also with Popa and Fielding[6] who have reported that the portal circulation drains the sinusoids of the pars distalis, ascends the infundibulum and breaks up into a capillary network within the hypothalamus.

The Absence of Lymphatic Drainage. — Presumably the hypophysis does not have a lymphatic drainage. Clark[6] states that there are no lymphatics in the brain and spinal cord so that the function of absorption must be accomplished by means of the veins. Drinker and Field[61] have remarked that lymphatics are found in practically all mammalian tissues with few exceptions, among which are "the depths of the central nervous system."

Possible Pathways of Hormonal Secretion and Adenohypophysial Stimulation. — No practical purpose can be served by recapitulating the circumstantial evidence and theories which have been recorded in connection with the possible pathways of secretion from the hypophysis. Rioch[64] has reviewed the available data in detail. One aspect of this problem which surprisingly has received little attention is the relation of the unique angio-architecture of this region to the problem of hormonal secretion in general and adenohypophysial stimulation in particular. For reasons which will be amplified elsewhere in this chapter, it is essential to regard the hypothalamo-hypophysial area as a functional unit.

The adenohypophysis is an endocrine organ and as such probably empties its secretion directly into the circulation. Since its dense plexus of sinusoids drain through the lateral hypophysial veins into the cavernous sinuses and through them into the systemic circulation, it is reasonable to assume that the hormonal secretions of the pars distalis leave the gland through this pathway. So far as the constituent parts of the infundibular system are concerned, there are two vascular channels which merit consideration. In the first place, the direction of the blood flow is by way of the portal circulation from the median eminence, pars tuberalis, pars infundibularis and infundibular stem into the sinusoids of the pars distalis. If all or a part of the hormonal secretions of these parts of the hypophysis leave the sinusoids of the pars distalis, the efferent blood vessels must direct them into the systemic circulation via the cavernous sinuses. Secondly, it is possible, although unlikely, that another secretory pathway is established through the connections of the plexiform capillary bed of the infundibular stem with the capillaries of the general brain net of the hypothalamic region. It is more probable, however, that the blood flow is in the opposite direction, i.e., from the hypothalamus

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Electrical stimulation of the rat's cervix induced pseudopregnancy in 76 per cent of normal animals in 88 per cent after bilateral cervical sympathectomy in 56 per cent after bilateral superior cervical sympathetic ganglionectomy and in 44 per cent after resection of the cervical sympathetic trunks and the third cervical ganglion nerves It is now clear that the superior cervical sympathetic ganglia are not essential to the mechanism of hypophysial gonadotropic activation, although apparently they are involved in it to some extent, possibly in connection with the third cervical ganglion nerves[69, 70]

The Vidian Ganglia and the Greater Superficial Petrosal Nerves — Some of the nerve fibers which pass from the carotid plexus to the hypophysis, are of other than cervical sympathetic origin[71] Chorobski and Penfield[3] have demonstrated the existence of a bundle of small myelinated and non myelinated fibers, which forms a part of the nervus intermedius of Wrisberg, but which leaves the facial nerve as part of the greater superficial petrosal before joining the carotid plexus Hair and Mezer[74] have investigated this pathway, which was endorsed by Hinsay and Markee as a likely possibility[75] They found[74] that electrical stimulation of the facial nerve at the geniculate ganglion did not induce ovulation in rabbits, nor did bilateral destruction of the facial nerve prevent post coital ovulation Zacharias[76] on the other hand has reported that either bilateral removal of the rat s vidian ganglion or section of the greater superficial petrosal nerves is followed by pseudopregnancy in all operated cases and coincidentally induces an increased insulin sensitivity in 66 per cent of the animals Zacharias regards the vidian ganglion as a source of part of the innervation of the adenohypophysis He originally investigated the nerve supply proximal to the sphenopalatine ganglion[7], because bilateral sphenopalatine ganglionectomy induced pseudopregnancy in 40 per cent of the rats operated on by Rosen, Shelesnyak and Zacharias[78] At the junction of the greater superficial petrosal nerve with the great deep petrosal nerve he found the vidian ganglion from which small branches are distributed to the sixth nerve to the internal carotid plexus, to the sheath and presumably to the parenchyma of the adenohypophysis

The Hypothalamus — Available evidence indicates that the hypothalamus is related functionally in an important way to the gonadotropic activity of the adenohypophysis The literature also contains ample reference to nerve fibers which arise in the hypothalamus and pass down the infundibular stem to the pars intermedia and the infundibular process Cajal[79] Tello[80], Croll[81] and Hair[71] are among those who have reported that a few of these fibers cross over into the pars distalis in certain mammals Brooks[7] has described fibers resembling nerve fibers in the pars distalis of normal rabbits which appear to enter the gland from the stalk likewise he has confirmed Croll s observations All anatomists however have experienced the difficulty, underscored by Rasmussen[8] of demonstrat

ing a significant number of nerve fibers in the pars distalis Whether or not this argues seriously against the functional significance of these fibers is an open question It might be pointed out however that the number of these fibers is relatively small in view of the importance of the gonadotropic activity which they are supposed to initiate and control

Physiological experiments with mated rabbits indicate that at one point in their course the nerve fibers carrying the coital stimulus reach the hypothalamus from whence stimulation of the adenohypophysis is affected How the latter is accomplished still is a matter for speculation Westman and Jacobsohn[3], Haterius and Derbyshire[84] and Harris have found that electrical stimulation of highly localized areas in the hypothalamus results in gonadotropic activation of the adenohypophysis with subsequent ovulation Brooks[7] has demonstrated that in the rabbit coital stimuli to the adenohypophysis are interrupted by resection of the infundibular stem Although Harris[85] and Brooks agree on the general course of this pathway they are not in accord on the systemic and endocrine effects of stem section Harris rabbits refused to mate and their gonads atrophied after transection of the stem whereas Brooks reported that in his rabbits the gonads were histologically normal and that the mating behavior was unaltered after a similar operation The extent to which the circulation to the adenohypophysis is interrupted by transection of the stem may have an important bearing on this discrepancy in the results of supposedly identical experiments As a matter of fact a partial interference with the essential blood supply to the hypophysis might account for Brooks results although Brooks believes that his observations constitute evidence for the existence of a neural pathway from the hypothalamus through the infundibular stem to the adenohypophysis Friedgood[89] has suggested that a humoral component arising in the hypothalamus or in the glandular tissues drained by the portal circulation of the infundibular or tuberal structures may be an important part of the mechanism which activates the gonadotropic function of the adenohypophysis

Clinical Interpretation of Phylogenetic Data

Introduction

It has been customary for the clinician to regard the hypophysis as a gland of internal secretion which from a physiological viewpoint is related closely to the other endocrine organs of the body The fact that the anatomical relations between hypophysis and cerebrum are so intimate was of interest almost exclusively to the embryologist and comparative anatomist although certain aspects of this juxtaposition came within the province of the neurosurgeon and roentgenol

ogist More recently, however, since the physiology of the hypothalamus has come under surveillance the spotlight of clinical interest has been shifted to the reciprocal functional relations, which exist between the hypophysis and the various hypothalamic nuclei and nerve tracts These viewpoints, important though they are individually and collectively, are quite likely to result in a limited con

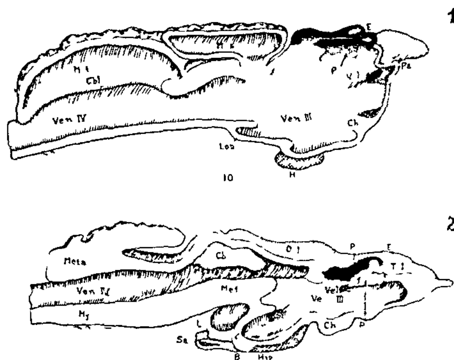


Fig 15 Reconstructions of adult Petromyzon (1) and Amia calva (2) mid sagittal view epi epiphysial complex chi chiasm cbl cerebellum hyp hypophysis loi inferior lobes met metencephalon meta metaphysis my myelencephalon mes mesencephalon lop posterior lobe opl optic lobe par paraphysis per periphysis tel endbrain vel transverse vellum ac accu va culosus vent III third ventricle vent IV fourth ventricle After Tilney

ception of the biological significance of the hypophysis cerebri A more adequate perspective of its biological importance ought to include some appreciation of the phylogenetic relation of the hypophysis to the whole system of cerebral glands, of which it is only one representative

The hypophysis is one of ten cerebral glands eight of which are derived from the roof of the brain and two of which make their appearance in connection with the floor of the brain (Fig 15) In a comprehensive contribution to, and resume

of this subject Tilney states that the endophyses as represented by the lateral mesial and caudal chorioidal glands are the only glandular structures which maintain a definite constancy of histological architecture and function among the outgrowths of the roof of the brain The other five cerebral glandular outgrowths in this group are the paraphysis the periphysis the epiphysial complex the mesophysis and the metaphysis The two glandular outgrowths which are derived from the floor of the brain are the hypophysis and the saccus vasculosus In contrast to the inconstancy which is observed in a phyletic study of the development and degree of specialization of most of the roof glands the hypophysis and saccus vasculosus are represented constantly in the vertebrate phylum from the earliest of cyclostomes through the highest of primates

Glandular Structures of the Roof of the Brain

The outgrowths of the roof of the brain have numerous interesting features a detailed discussion of which is quite beyond the scope of this writing These cerebral structures have two characteristics in particular however which merit special consideration All of them show a typical glandular structure at one time or another in their phyletic history and one or more of them is responsible for the secretion of the cerebrospinal fluid Of the eight cerebral glands which are derived from the roof of the brain only the three chorioidal structures maintain a constant functional representation in the various phyla and consequently they must be of special biological importance The paraphysis and periphysis are similar in structure to the chorioidal glands but they exhibit only inconstant phyletic representation The present discussion is being limited to a consideration of the chorioidal paraphysial and periphysial cerebral glands

The Lateral Mesial and Caudal Chorioidal Cerebral Glands — In lower animals the roof plates of the telencephalon and rhombencephalon remain undifferentiated and are referred to as the anterior and posterior tela chorioidea respectively In higher vertebrates the ventricular cavities of the brain are surrounded by a thick and massive wall of nervous tissue except in the regions which correspond to the tela chorioidea of the lower forms Here the wall retains its embryonic character in the form of a thin non nervous epithelium the lamina epithelialis Adherent to the outer surface of the lamina epithelialis is a highly vascularized pia mater The pial connective tissue and its widely dilated capillaries and venous sinuses invade and indent the tela chorioidea early in its ontogenetic development thus throwing it into crumpled folds and tufts These are invaginated into the ventricular cavities so that a relatively large free surface with branching villus like processes of tortuous vessels and a rich capillary net is exposed to the ventricular system and its fluid These are the chorioid plexuses

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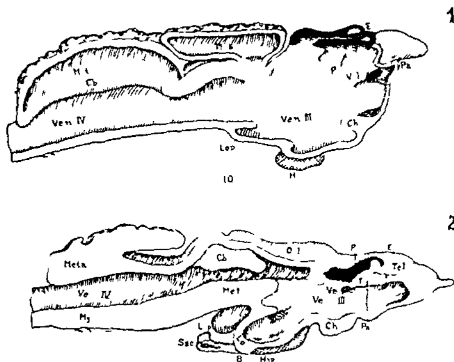


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It is now generally recognized on the basis of embryological histological pharmacological pathological and clinical observations that the cerebrospinal fluid is formed by the chorioid plexuses of the brain ventricles [87 88 89 9 91] Weed[9 93] has demonstrated that the formation of cerebrospinal fluid in the embryo appears coincidentally with the differentiation of the chorioid plexus from the ependymal cells Faivre[94] and others who have confirmed him[95 96 9] have presented evidence of the secretory character of this epithelium The epithelium of the chorioid plexus acquires a unique structure early in its development which differs from that of the ependymal cells lining the ventricles The chorioidal epithelium contains glycogen and carries cilia in its embryonic stages In the adult its cells are cuboidal and are arranged in a single regular layer with definite internal and external limiting membranes (Fig 16) They contain a varying number of rod shaped and granular fuchsin staining bodies which appear to be mitochondria and a round central nucleus Large transparent vacuoles or large usually single fat droplets are very common inclusions in the distal part of the cells Some investigators have observed a brush border on the free surface of these epithelial cells The epithelium of the chorioid plexuses is said to store large amounts of trypan blue in granular form after repeated intravenous injections of the dye into animals

The autonomic innervation of the chorioid plexus has been studied by Clark[98] and Stohr[9] who observed that the nerves penetrated to the epithelial layer and ended on the epithelial cells The latter may be of functional significance but there is no evidence available on this point Finesinger and Putnam have demonstrated that stimulation of the cervical sympathetics causes constriction of the vessels of the chorioid plexus in the cat, whereas stimulation of the vagus leads to their dilatation

From a phyletic viewpoint Minot [1] suggests that the roof of the primitive forebrain gives rise to a series of secreting structures which are directly connected with the formation of fluid in the cavities of the brain In his opinion the chorioidal glands supply the main bulk of this fluid

The Paraphysis — The paraphysis (See Fig 15) is a midline outgrowth from the cephalic extremity of the roof plate of the forebrain It is a structure which is common to all vertebrates either in the adult or in the embryonic state The course of its phyletic development is traced by a curve which rises steadily from the cyclostomes through the fish reaches its peak in the amphibia and descends through the reptiles and birds to its lowest degree of differentiation and specialization in the mammals In the amphibian necturus the paraphysis is a lobulated structure which lies just beneath the pia where it is covered by blood vessels At first it was regarded mistakenly as a part of the chorioid plexus because it was so vascular and so close anatomically to this structure Minot s observations in

which are to be found in the roof of the fourth ventricle, the roof of the third ventricle and in part of the wall of each lateral ventricle When the meninges of the brain are removed at autopsy, the chorioid plexus of the roof of the fourth ventricle may be torn away leaving a large opening, the fossa rhomboidalis The

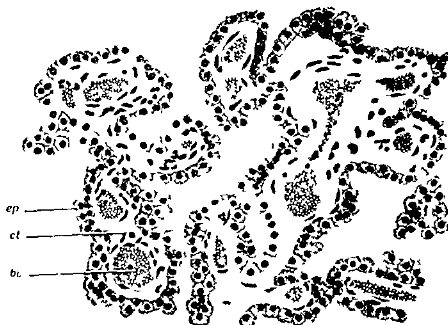


Fig 16 Chorioid plexus of the fourth ventricle from man ep epithelium ct connective tissue bv blood vessels 190 x After Maximow

fourth ventricle communicates freely with the subarachnoid space through the two foramina of Luschka one of which is located in each of its lateral recesses The chorioid plexus of the fourth ventricle extends into each of the latter and protrudes slightly through the foramina of Luschka into the subarachnoid space The mid line third ventricle which leads into the fourth ventricle through the narrow aqueduct of Sylvius also communicates with the lateral ventricles of each hemisphere by way of the foramina of Monro The chorioid plexus of the third ventricle is continuous with that of the lateral ventricles at the foramina of Monro From this point the chorioid plexus extends posteriorly into both lateral ventricles following the curve of the caudate nucleus and fimbriae of the fornix inferiorly and anteriorly to the tip of the temporal horn The anterior and posterior horns of the lateral ventricles do not contain a chorioid plexus

kind or period of life but have been common to all vertebrates from the beginning to the end of their history It is this keystone position which the hypophysis and saccus vasculosus occupy The activities of these organs have constituted an unchanging stream of endocrine function Their long established structural constancy is indicative of their indispensable nature just as their complex differentiation implies the possibilities of widespread tropic influences

Physiological Significance of the Cerebral Glands from a Phyletic Viewpoint

In a comprehensive discussion of the phyletic and embryological aspects of roof glands of the brain Tilney leaves untouched the problem of their physiological significance except in so far as he points out that certain of these structures are concerned with the formation of cerebrospinal fluid

There are two opposing theories concerning the method of formation of the cerebrospinal fluid Faivre[94] and Luschka[9] claimed that it was secreted by the parenchymal cells of the chorioid plexus whereas Mestrezat[108] maintained that the chorioid plexus acts as a dialyzing membrane and that the cerebrospinal fluid is a dialysate in equilibrium with the blood plasma There are a number of telling points against the dialysate theory The latter does not account for the histological tructure of the cells of the chorioid plexus nor for the changes that take place in these cells during conditions which induce a more rapid formation of cerebrospinal fluid Moreover the composition of the cerebrospinal fluid i not identical quantitatively with that of filtrates produced artificially or with dialysates of plasma although the cerebrospinal fluid is isotonic with blood plasma and tends to remain in osmotic equilibrium with the blood when the latter is altered experimentally or by disease[109 1 0 111] Furthermore the dialysate theory does not explain the unequal di tribution between blood plasma and cerebrospinal fluid of calcium, potassium phosphate uric acid creatinine amino acids glucose and magnesium[112] nor does the distribution ratio of sodium chloride and bicarbonate between plasma and cerebro pinal fluid satisfy the Donnan theory quantitatively The fact that variations in the plasma level of glucose urea chloride lactic acid and alcohol are associated with parallel changes in the cerebro pinal fluid suggests that these substances are subject to filtration On the other hand the distribution of ingested bromide between blood plasma and cerebro pinal fluid is not readily explained by the dialysate theory

In view of certain of the foregoing data, and because there are volume and pressure changes in the cerebro pinal fluid in response to hydrostatic and osmotic variations in the blood one must assume that osmotic and hydrostatic forces play a role in the formation of the cerebro pinal fluid Contrary to general belief however there is no evidence to warrant the assumption that the cells of the

rana[101] have disclosed that the paraphysis has an epithelial structure, a tubular arrangement and a sinusoidal circulation The glandular character of its parenchyma is obvious in all other forms which have been studied[10 103 104 105 106 107] Tilney suggests that the glandular specialization of the paraphysis indicates clearly that it may provide a secretion of special chemical substances for the cerebrospinal fluid

The Periphysis — The periphysis (Fig 15) is a highly vascular paired out growth from the roof of the forebrain, which develops from the dorsal sac just caudal to the paraphysis It is a large sac like structure, whose thin convoluted walls consist of one or two layers of epithelium with many irregular communicating diverticulae In general the sacs resemble the chorioidal glands and are surrounded by a rich vascular network formed by a plexus of capillaries The periphysis reaches its peak of development and differentiation in the ganoids or fish but it may be recognized in vestigial form among amphibia reptiles, birds and man

Glandular Structures of the Floor of the Brain

The Hypophysis and Saccus Vasculosus — In other sections of Part I the reader will find a fairly complete account of what is known concerning the ontogenetic development of the hypophysis and saccus vasculosus The phyletic aspects of this subject matter have been dealt with in detail by Tilney[1] For our present purposes it is adequate to record a summary of Tilney's lucid thoughts in this direction

It is relatively simple to trace the different parts of the hypophysis cerebri and saccus vasculosus through the entire line of vertebrates in each of which they maintain a high degree of specialization The constant representation of the hypophysis throughout this phylum is equally true of its occurrence, of its origin and development of the biotaxis of its neural and somatic ectodermal anlage, of its relations to the brain and skull and of the final differentiation of its structure and cellular constituents The regularity with which these complicated and relatively numerous structural elements reappear throughout this phylum is suggestive of a specific functional significance even though certain minor variations in pattern do occur

Tilney believes that 'the contrast between the variability of the cerebral glands connected with the roof of the brain and the constancy of the floor glands has undeniable significance On the one hand the glandular specialization bespeaks an adaptive differentiation to meet the exigencies of life peculiar to a species a family or order of animals on the other this specialization is in the interest of certain dominating themes of existence which are confined to no single

kind or period of life but have been common to all vertebrates from the beginning to the end of their history It is this keystone position which the hypophysis and saccus vasculosus occupy The activities of these organs have constituted an unchanging stream of endocrine function Their long established structural constancy is indicative of their indispensable nature just as their complex differentiation implies the possibilities of widespread tropic influences

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chorioidal plexus do not secrete a significant proportion of the cerebrospinal fluid As a matter of fact the available phylogenetic data support this possibility strongly

In general it is important to note that, by definition, all of these cerebral structures are glands of internal secretion at one or more points in their phyletic history Although this has not been established physiologically as yet the histological evidence is consistent with this interpretation, inasmuch as these structures are characterized by a typical secretory parenchyma Moreover it is of significance in this connection that several of the cerebral glands, which take origin from the roof plate of the forebrain are responsible for the secretion of the cerebrospinal fluid The cerebrospinal fluid may be regarded therefore, as the product of a gland of internal secretion even though its rate of secretion may be affected by hydrostatic and osmotic variations in the blood plasma This conclusion which is suggested by the phylogenetic data indicates that the cerebrospinal fluid may have a hormonal action in addition to discharging the excretory nutrient and mechanical functions which have been ascribed to it heretofore Whether or not this hypothesis is established by future investigations is of small consequence as compared with the conception that clinical correlations between structure and function may be found among the observations recorded by students of phylogeny

The phylogenetic history of the chorioidal cerebral glands, which are as constantly represented in the various vertebrates as the hypophysis itself may hold biological secrets which are unfathomed as yet If the advances which have been made in the physiology and biochemistry of the hypophysis are any indication, there is much promise in the further search for the endocrine functions of the other cerebral glands

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PART II

CYTOPHYSIOLOGY AND BIOCHEMISTRY OF THE ADENOHYPOPHYSIS

ADENOHYPOPHYSIAL CYTOLOGY AND ITS FUNCTIONAL SIGNIFICANCE

Cell Types

The foregoing embryological studies have disclosed that a complex glandular organ consisting of pars distalis pars intermedia pars infundibularis and pars tuberalis develops from an undifferentiated stomodeal epithelium The embryonic cells of these glandular divisions differentiate into specific and characteristic cell types which include the chromophobes acidophiles and basophiles The cytoplasm of the chromophobes is devoid of granules the cytoplasmic granules of the acidophiles have a strong affinity for the acid dyes and the cytoplasmic granules of the basophiles take the basic dye but their granules are less distinctly tinted and are more irregular in outline and size than those of the acidophiles[1 2] The four subdivisions of the adenohypophysis exhibit somewhat similar cytological characteristics but certain individual variations of possible importance have been recognized

Pars Distalis — According to Tilney the pars distalis is comprised of two distinctly different regions viz an outer cortical zone and an inner or central core which is almost completely invested by the cortex The histological differences between the two portions of the pars distalis are said to be distinct In general the cortical zone has a much lighter staining reaction and consists essentially of basophiles among which are scattered numerous chromophobes The cellular arrangement is in the form of large acini and extensive interacinal cell masses The medullary or central zone consists of smaller and more compact acini and the interacinal cell masses are more limited The individual cells stain more deeply than those in the cortex and are acidophilic predominantly The cells in both zones are polygonal in shape and the acini of which they are a part are surrounded completely by a connective tissue capsule

Pars Intermedia — The parenchyma of the pars intermedia is the smallest part of the human hypophysis comprising 0 13 to 3 64 per cent of the total hy

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Cell Counts

Although the three cell types occur in definite proportions there is great individual variation in this respect as well as in the arrangement and location of the cells within the pars distalis of the adenohypophysis Consequently cell counts must be made in accordance with statistical methods Rasmussen s classical studies for the human gland[14 3] show that for the adult male the average normal proportions of cells are 5 2 per cent chromophobes 36 8 per cent acidophiles and 10 9 per cent basophiles In different individuals the chromophobes varied from 34 to 66 per cent and acidophiles from 23 to 59 per cent and the basophiles from 5 to 27 per cent In the adult female the average normal proportions of cells are 49 6 per cent chromophobes 43 4 per cent acidophiles and 7 per cent basophiles The chromophobes vary from 33 to 74 per cent the acidophiles from 19 to 58 per cent and the basophiles from 3 to 16 per cent The relative proportions of cells in most species is approximately the same These data indicate that the basophiles constitute less than 10 per cent of the cells in the pars distalis and are significantly more numerous in males than in females The acidophiles represent about two fifths of all the cells and are definitely more numerous in females The chromophobes account for about 50 per cent of the total cell count The males have slightly more chromophobes than the females Although this sex difference is small it is just significant statistically

Statistical surveys of the cell population and specific cytological methods have disclosed that certain physiological states are associated with a significant shift in the relative proportions of the three cell types and that physical changes occur in the cells themselves at these times Such deviations from the normal have been noted after castration during and after pregnancy [5] and after thyroidectomy [6] Changes in cytoplasm and cell proportions likewise have been correlated with the estrus cycle [7 1 7] and with secretion of the luteinizing and lactogenic hormones[15 8] and after the parenteral administration of various hormones to normal and abnormal animals Observations such as these have contributed also to a better understanding of the complex genetic interrelations of the three cell types

Interrelations of Chromophobes Acidophiles and Basophiles

The rarity of mitotic divisions in the adenohypophysis precludes the development of enough hyperplasia to change the relative proportions of cells It is generally believed therefore that one specific cell type changes into another but there is still considerable controversy about the modus operandi of this transformation The most convincing evidence favors the theory according to which the chromo

pophysis according to Rasmussen[3] It is bounded anteriorly by the hypophysial cleft which is open in the human during childhood and adolescence but becomes subdivided later into numerous loculi of different size by trabeculae of flattened cuboidal epithelial cell These loculi become filled with secretion from tubulo racemose glands which arise in the pars intermedia and invade the processus infundibuli Further details of related histological data will be found in the section on neurohypophysial cytology in Part V

There are several other types of cells in addition to those which comprise the epithelium of the hypophysial cleft and tubuloracemose glands Basophilic cells constitute the major portion of the parenchyma and are arranged in long columns or cords which interdigitate with the neurohypophysial tissue in many areas The virtual absence of acini or aciniform grouping of cells also characterizes this part of the gland Chromophobes and acidophiles are scattered among the basophiles The latter occur particularly among the ciliated cells which have been described in the human as well as the subhuman species by Peremeschko[10], Kiyono[11], Guizzetti[1] Bryant[13] Rasmussen[14] and Friedgood and Dawson[15] Another cell seen in the pars intermedia is the so called ependyma like cell[16 1 18 19] It is impregnated best by Golgi s method and consists of a small ovoid nucleus midway between its two extremities Two processes extend from the cell body, one in the direction of the anterior and the other toward the posterior boundary of the pars intermedia

Pars Infundibularis — The cellular constituents of this subdivision of the adenohypophysis have not been studied adequately enough to warrant more than passing comment Without differentiating pars intermedia from pars infundibularis Tilney[7] states that the latter is composed only of basophilic cells

Pars Tuberalis — The pars tuberalis is equal or nearly equal in size to the pars intermedia according to the quantitative studies of Atwell Its general histological structure appears to be that of a coarse network of cell cords and in some animals a striking feature is the presence of numerous alveoli The author has not encountered a clear cut statement on this latter point with reference to the human hypophysis Chromophobes constitute the predominant cell type, although basophiles also are present and acidophiles are rare Wolf and Cleveland[1] and Dawson and Friedgood point out however, that the physiological state of the hypophysis may determine whether chromophobes or basophiles predominate In the rabbit occasional acidophiles and numerous basophiles are to be found in the tongue like projection of the pars tuberalis as it passes toward the hypothalamus in front of the infundibular stem[15]

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phobes are transformed either into acidophiles or basophiles through the accumulation of the corresponding specific granules[?, ?, ?] Apparently certain chromophobes are themselves so highly type specific that they give rise only to one or the other of these chromophilic cells There is no evidence to support the belief that a transitional bigranulated cell exists or that an acidophile can change into a basophile or vice versa If the chromophilic granules of a given cell should be interchangeable it is believed that this transformation must occur during the stage of the undifferentiated chromophobe[19]

Physiological Significance of Chromophilic Granulation Theories of Hormone Elaboration and Secretion

The transformation of chromophobes into chromophilic cells and vice versa is associated with a change in the physiological state of the organism, the presence of chromophilic granules indicates that the cell is functionally active, whereas the chromophobe represents an inactive reserve or parent cell It is believed generally that the chromophilic granules represent the hormone either in a stored or active form and that degranulation of a cell occurs coincidentally with the phenomenon of secretion Direct evidence on this point was secured by Friedgood and Dawson[15, 31, 3] in connection with their observations on the elaboration and secretion of the luteinizing hormone from the adenohypophysis

Of the large number of adenohypophysial hormones which have been postulated only seven are accepted generally These are the growth hormones the follicle stimulating luteinizing and lactogenic hormones the thyrotropic hormone the adrenocorticotropic hormone and the diabetogenic hormone Since these numerous tropic substances are elaborated only by the basophiles and acidophiles the situation often is viewed with considerable despair and incredulity However, if one considers the accomplishments of the hepatic cell which is concerned with the most complex of chemical activities affecting every known phase of metabolism the performance of the adenohypophysial chromophiles is not uncommonly spectacular Apparently a number of independent albeit related and integrated, biochemical and physiological activities may coexist in a highly differentiated cell

Relatively little is known concerning the chemistry of the adenohypophysial hormones and practically nothing has been discovered of their chemical interrelations and elaboration They could be manufactured and secreted as chemically independent molecules they might be attached to a large protein molecule in the form of prosthetic groups or one hormone could affect a number of different endocrine glands depending on the specific end organs or target glands with which it came into contact The latter possibility can be eliminated from consideration because of the fairly quantitative chemical separation of the lactogenic

thyrotropic somatotropic and gonadotropic hormones If the second hypothesis represents the true state of affairs an unusual demand for one of the hormones would be answered by the indiscriminate overproduction of several other tropic substances which happen to be attached to the same protein molecule Such an inelastic physiological mechanism always would create overfunction of a number of related endocrine glands to the disadvantage of the organism as a whole There might be one conceivable advantage to such a system viz if the metabolic demands created by hyperactivity of one target gland could be maintained only by increasing the functional activity of several other intimately related glandular structures

As a matter of fact this multiple type of response is encountered not infrequently in various clinical disorders of the hypophysis of which acromegaly and the menopause are good examples In acromegaly the primary disability is caused by an overproduction of the somatotropic hormone with which often there is associated an abnormally increased secretion of the diabetogenic hormone the thyrotropic hormone and the ICSH or luteinizing hormone resulting in diabetes *mellitus hyperthyroidism and hypergonadism respectively* *The primary adeno hypophysial* dysfunction of the menopause is expressed in terms of overproduction of the follicle stimulating hormone but hyperthyroidism and diabetes mellitus not infrequently are concomitant complications of this condition These complex endocrine patterns of activity can be explained also on the basis of the first hypothesis inasmuch as the activation of one phase of a cell s metabolism might conceivably result in hyperactivity of a closely related but chemically independent functional unit of the same cell The clinical cour e of disordered function of the acidophiles in acromegaly actually favors the first hypothesis since the thyrotropic and gonadotropic functions of the e cells are not necessarily disturbed in the same direction nor at the same time It is possible therefore that a single cell type may elaborate a number of metabolically and chemically related hormones which are secreted independently as the occasion demands This hypothesis would explain satisfactorily why a disturbance in the elaboration and secretion of one of these hormones may on occasion induce repercussions in the metabolism and secretion of other hormones which originate within the same cell

The Gonadotropic Hormones

Chemistry

The three adenohypophysial secretions which contribute to the regulation of gonadal function are the luteinizing follicle stimulating and lactogenic hormones Significant progress has been made in their chemical characterization but still

there is much to be learned Although chemically impure these substances can be separated from each other and from the remaining known adenohypophysial hormones in highly purified states The follicle stimulating hormone, also known as FSH or thylakentrin appears to be a glycoprotein with an isoelectric point at about pH 4 8[4] Chemical analyses of the luteinizing hormone, otherwise referred to as LH, metakentrin interstitial cell stimulating hormone or ICSH, are being done on sheep and swine hypophyses by three groups of investigators A highly purified glycoprotein has been isolated from each animal, but the chemical characteristics of these substances are unlike enough to indicate the presence of two different proteins The sheep protein, isolated by the University of California group contains 4 5 per cent mannose, 5 8 per cent, glucosamine, 1 per cent tryptophane 4 5 per cent tyrosine and 5 4 per cent cystine Thus far it has been found that the swine protein isolated by the Rockefeller Institute and Squibb groups contains only 2 per cent carbohydrate and 3 8 per cent tryptophane The isoelectric point of the sheep protein is at pH 4 6, while that of the swine protein is at pH 7 4[11] The lactogenic hormone also called prolactin galactin and mammotropin was the first adenohypophysial substance to be secured in a highly purified state A crystaline protein has been obtained from a highly purified preparation of the lactogenic hormone[4] In the case of proteins, however the crystalline state is not considered adequate evidence of purity The electrophoretic behavior solubility studies and ultracentrifugal analysis of a highly purified amorphous preparation of prolactin indicate that it is a homogenous protein[42] The isoelectric point appears to be at about pH 5 65[43] The crystalline and purified preparations of prolactin give the usual protein color tests viz biuret xanthoproteic Millon s and Hopkins Cole The labile sulfur test is positive, qualitative tests for phosphorus and for carbohydrates are negative There is no indication of the presence in the molecule of any of the common types of prosthetic groupings Beef prolactin contains 51 50 per cent carbon 6 92 per cent hydrogen 16 50 per cent nitrogen 2 00 per cent sulfur, 5 7 per cent tyrosine, 1 3 per cent tryptophane and 3 4 per cent cystine

Physiology

The Follicle stimulating and Luteinizing Hormones — The follicle stimulating hormone also known as FSH or thylakentrin is a gametogenic substance, which is essential for the growth of graafian follicles and stimulates the sperm forming tissue of the testes[44 4 46] Acting in conjunction with FSH is the luteinizing hormone also known as LH ICSH or metakentrin which is essential for the secretion of estrogens from the ovarian follicles[47 48 49] and for the various consecutive phases of follicular development including the primordial follicular antra

the progressive preovulatory enlargement of the ovarian follicles ovulation and the formation of luteal tissue and corpora lutea[1 6 35 5] The luteinizing hormone is not the factor however which maintains the corpora lutea in a functional secretory state another adenohypophysial luteotropic factor prolactin is responsible for that function[6 57 58] A highly purified fraction of follicle stimulating hormone containing traces of luteinizing hormone induces the development of normal estrous follicles and mating behavior in young adult anestrous cats[9] In the male LH acts on the intersitial cells of the testes stimulating them to secrete the male hormone which then maintains the secondary sex structures and characteristics of the organism[61]

That the gonadotropic hormones of the adenohypophysis may be involved in the development of ovarian tumors in the hen which resemble the arrhenoblastomata of women *is suggested by studies of the ovaries of hens in whom sex reversal* occurred spontaneously[6] Available evidence indicates that the growth of these tumors in the hen was induced by the pathological destruction or atrophy of the left ovary which is equivalent to complete castration in this animal It is believed that the latter is responsible initially for hypertrophy of the adenohypophysis The subsequent increase in secretion of the gonadotropic hormones stimulates the vestigial cells of the atrophied medulla of the right ovary which becomes active functionally The androgenic effect of the ovarian secretion thus induced *culminates in the sex reversal*[60]

The Luteotropic Hormone — The chief functions of prolactin were thought originally to be crop gland proliferation in pigeons and initiation of lactation in mammary glands possessed of a certain degree of alveolar development[3 64 65 66 67] Subsequent studies have indicated however that there is an increased secretion of the adrenocorticotropic hormone as well as prolactin subsequent to pregnancy[68] The initiation of lactation apparently depends on the synergistic action of prolactin and a hormone of the adrenal cortex[65 6 7 1] Prolactin has been shown to exhibit a number of other effects but the latter are species specific in many instances and cannot be transferred from pigeons on which most of the studies have been done to the various mammalian species[6] More recently it has been demonstrated that prolactin has a luteotropic function whereby it maintains the functional integrity and secretion of the corpora lutea which otherwise would regress under the influence of LH alone[56 57 58 7]

Cytology in Relation to Secretion

The Castration Cell — Ablation of the ovaries or testes is followed regularly by an increase in the size and number of the basophiles in the adenohypophysis of the rat guinea pig rabbit goat monkey and man[4 39 73 74 5] The cytoplasm

of certain of these enlarged basophiles becomes vacuolated and is displaced by a colloid like material which also pushes the nucleus to one side This cytological change imparts the typical appearance to the so called " castration cell " or " signet ring cell [73, 4] which does not develop in some species, such as the guinea pig rabbit and man The physiological castration, which comes with advancing years in men and women likewise is associated with a significant increase in the percentage of basophiles [4]

Surgical and physiological castration also affect the acidophiles of the various aforementioned species including man The acidophiles are somewhat decreased in number and show regression toward the chromophobic state with a decrease in their size and staining capacity [3, 76, 7, 78]

The physiological significance of these cytological changes has been disclosed by a number of investigators in the course of quantitative and qualitative studies of the gonadotropic hormone content of the adenohypophysis of the blood and of the urine in the post castration period The gonad stimulating potency of the adenohypophysis of the castrated rat guinea pig and rabbit was found to be increased [9, 80, 81, 82, 83, 84, 8, 86] It was demonstrated, furthermore, that castration greatly increases the FSH but does not alter significantly the LH content of the adenohypophysis[87, 88, 89, 90, 91] A sex difference with regard to the latter was reported by Lipschutz and Villogran[9] who observed that castration does not change the luteinizing power of the male hypophysis, which already is rich in LH, but does increase it in the female in which normally it is very low

This increase in the FSH content of the adenohypophysis is associated with the appearance in the blood and urine of larger than normal amounts of FSH Experiments with parabiotic rats[87] show that the hypophyses of castrated males secrete chiefly the follicle stimulating hormone FSH Emery[93] demonstrated FSH in the serum of castrated rats but could not find it in their urine with his technic Jeffcoate[94] found FSH in the urine of 3 out of 5 castrated rabbits Fluhmann[95, 96, 97] discovered significantly increased levels of FSH in the serum of castrated and menopausal women Zondek[98] and Saethre[99, 100] demonstrated relatively large amounts of FSH in the urine of castrated and menopausal women respectively, and Hamburger[101] and Osterreicher[10] reported similar results for castrated and elderly men respectively Fluhmann and Hamburger emphasized that their extracts were predominantly follicle stimulating with negligible luteinizing qualities With extremely high doses it has been demonstrated however that luteinization of the ovaries of hypophysectomized rats can be induced by extracts of the blood and urine of castrated and menopausal women[103]

Correlation of the foregoing cytological and physiological data indicates that FSH is secreted by the basophiles The cytological appearance of the basophiles is, however more compatible with an increased accumulation of hormone rather

than with an acceleration in the rate of liberation of their secretion Consequently it is probable that the relatively large number of secreting basophiles in the hypophysis of the castrated individual is responsible for the excessive amounts of FSH which appear in the blood and urine after castration or during the menopause One must conclude also that small amounts of LH still continue to be released from the hypophysis of castrated individuals Although the source of FSH is generally agreed upon there is relatively little in the literature on the origin of LH and prolactin Friedgood and Dawson[13 14 33] have demonstrated however that LH is secreted by an acidophilic type of cell and their circumstantial evidence indicates that prolactin is derived from a cell with identical morphological characteristics

The Carmine Cell — The origin of LH was traced directly to the acidophiles by correlating the sequence of cytological and physiological events in the adenohypophysis with the characteristic effects of this hormone on the mature ovarian follicles of the cat and rabbit[5 34 3] The hypophyses were subjected to formol sublimate fixation followed by differential staining with Heidenhain s azan modification of Mallory s connective tissue stain Although the morphological appearance of the acidophile which secretes LH differs remarkably from the ordinary acidophiles it is not a new type of cell except in so far as it represents a hitherto unrecognized functional phase of the secretory cycle of the acidophiles When fixed and stained with the aforementioned technic[4 5] this cell takes a deep dark red stain whereas the ordinary acidophiles are orange the basophiles are deep or light blue and the chromophobes are light pink to colorless Because the cell contains large coarse irregular granules with a striking affinity for the azocarmine dye which is extracted readily from the ordinary acidophile it has been named the carmine cell The conditions under which it was discovered are somewhat as follows

Rabbits normally ovulate 10 to 12 hours post coitum and ovulation does not occur spontaneously in this species It has been demonstrated that post-coital ovulation can be prevented if (a) the infundibular stem is severed prior to mating or if (b) the hypophysis is removed within 60 to 90 minutes after mating Hypophysectomy does not interfere with ovulation if it is done later than 90 minutes post coitum These observations show that the behavioral phenomena which are characteristic of coitus induce ovulation in the rabbit by virtue of their stimulating effect upon the gonadotropic activity of the adenohypophysis It has been demonstrated furthermore that the gonadotropic potency of the hypophysis changes abruptly after mating The adenohypophysis of the average normal rabbit in heat contains 1 560 rabbit ovulating units of gonadotropic substance Within the half hour post-coitum there is a 20 per cent decrease in its gonadotropic potency to 1 2 0 units and after 4 hours post coitum the potency de

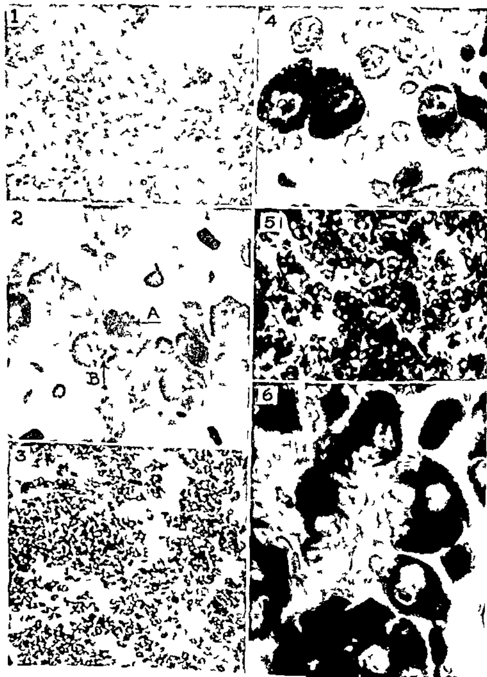


FIG 17 For legend ee page 828 (37)

creases approximately 87 per cent to a value of 210 units[1] These facts indicate therefore that within one and one half hours the adenohypophysis secretes the amount of gonadotropic hormone necessary to accomplish ovulation 10 hours later

Cytological evidence of this adenohypophysial stimulation by coitus was reported by Friedgood and Dawson in 1937[106] They found that the carmine cells are present in moderate number in the adenohypophysis of the estrous rabbit become increased significantly in number within one half hour after mating and reach their peak within 3 hours after which degranulation begins (Fig 17) This increase in number could be detected macroscopically in many instances because of their aggregation into compact irregularly circumscribed areas (Fig 18)

I was demonstrated subsequently that similar cell occur in the hypophysis of the cat an animal which like the rabbit usually ovulates only post coitum (Fig 19) Although morphologically different from those described in the rabbit s hypophysis these cells had an identical affinity for azocarmine Studies of the functional significance of these carmine cells revealed that they were not present in the hypophysis of the anestrous cat (Fig 19 (1) and (2)) They appear first in a limited area of the adenohypophysis during proestrus and then increase significantly in number and extent of distribution during estrus After mating they are arranged in a characteristic alveolar pattern and their greatly increased number and extent of distribution reach a maximum within 5 to 6 hours (Fig 19 (3) and (4)) Degranulation which occurs as early as 4 hours post coitum becomes more pronounced after 6 hours and the carmine reaction is virtually over at 14 hours

More specific information concerning the functional significance of the carmine cell was found in other experiments In most cats coitus normally induces ovula

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An area from the adenohypophysis of a rabbit in estrus showing the characteristic distribution of the carmine cells (black) in an unstimulated gland X 80 (2) A small cluster of carmine cells (dark) with a few orange acidophiles (gray) from an unstimulated gland showing the relative size of the 2 types of cells and the differences in the character of their granulation A lightly stained carmine cell is shown in mitosis (A) Note the distinct macula (B) in 3 carmine cells X 700 (3) An area from the adenohypophysis of a rabbit 1½ hour after mating shown the increase in size and number of the carmine cell and the general pattern of their distribution (cf (1)) X 80 (4) An area from the adenohypophysis of a rabbit in estrus showing the occasional large coarsely granulated carmine cells (black) which occur in association with smaller more finely granulated acidophile cells (gray) X 700 (5) An area from the same gland as (1) showing a dense aggregation of carmine cells with scattered orange acidophiles X 160 (6) An area from an activated gland showing densely stained carmine cells (black) and orange acidophiles (gray) X 700

Tissues in (1) and (4) were fixed in formalin The others were fixed in mercuric bichloride and formalin All were stained by Heidenhain s azan modification of Mallory s method Reproduced from Endocrinology 1938 XXII 674

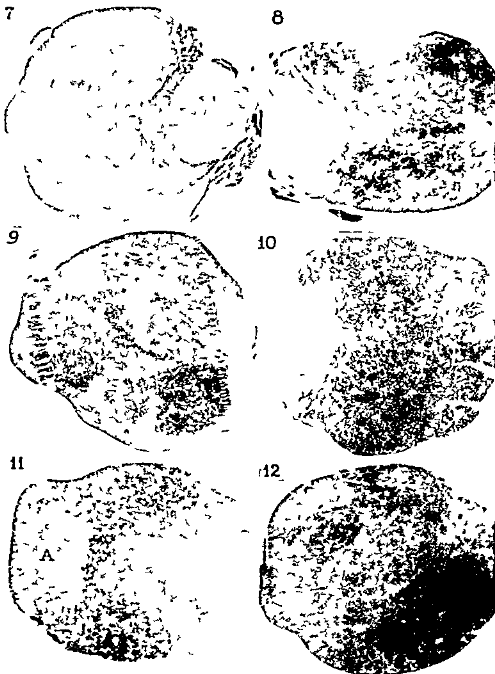


Fig 18 For legend see page 828 (39)

tion within 26 to 30 hours but this does not occur if the animals are subjected to various non specific abdominal operations shortly after mating[1] In such circumstances the usual post-coital carmine cell reaction is absent and the number of carmine cells remains at the average estrous level[1] Furthermore there is a marked delay in the onset of degranulation inasmuch as the granulation of the carmine cells of animals autopsied 48 hours or more post-coitum is comparable to that of the estrous cat The extent of the carmine cell reaction alone cannot be correlated however with the secretion of the gonadotropic substance since a careful study in serial section of the ovarian follicles failed to reveal evidence of activation unless adequate degranulation was observed also The occurrence and amount of degranulation apparently is the factor which determines whether or not maturation of follicular ova and ovulation will occur Lack of degranulation of an extensive carmine cell reaction leaves the ovarian follicles in an estrous state partial degranulation may or may not be associated with minimal evidence of maturation depending on the original extent of the carmine cell reaction massive degranulation of a widespread carmine cell reaction appears to be essential for completion of maturation and subsequent ovulation

On the basis of these and other published observations Friedgood and Dawson[15] have concluded that (a) the carmine cell reaction constitutes histological evidence of the enhanced gonadotropic activity of the adenohypophysis which results from coitus (b) that the carmine cell contains a luteinizing hormone which is essential for the initial maturation and subsequent ovulation of the ovarian follicles (c) that degranulation represents the secretory phase during which if the extent of the carmine cell reaction is sufficient and the degranulation adequate enough hormone is released to initiate maturation and to induce ovulation

Although these data indicate that in the post-coital period the carmine cells are related to elaboration and secretion of the luteinizing hormone it is believed[35] that they may be associated also in some way with other gonadotropic functions of the adenohypophysis since they are present in extraordinarily large numbers in the cat s hypophysis during the last week of pregnancy and early lactation

The Pregnancy Cell —Contrary to a generally accepted theory [8] the hy

(7) A representative section of an unstimulated hypophysis showing the uniformity of the cellular distribution in the pars distalis X 20 (8) A section from the hypophysis of a rabbit 45 minutes after mating showing distinct and irregular dense areas of carmine cells X 20 (10) A section from the hypophysis of a rabbit 5½ hours after mating The cellular aggregations are not so large and distinct This results in a mottled appearance X 20 (11 and 12) Sections of other activated hypophyses showing variations in the distribution of the carmine cells In (11) the median antero ventral area zona tuberalis (A) is distinctly outlined X 20 Black areas represent sites occupied by the carmine staining cells Reproduced from Endocrinology 1938 XXII 6 4

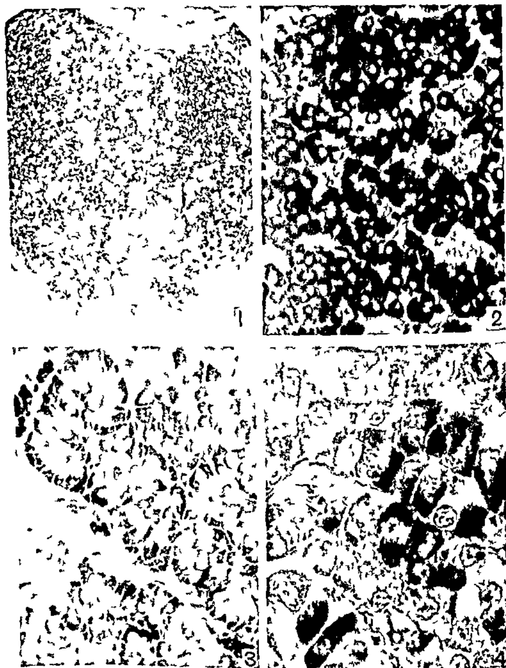


Fig 19 For legend see page 828 (41

pophysis appears to be an actively secretory gland during pregnancy Degranulation of the acidophiles and basophiles numerous mitochondria and hypertrophy of the Golgi apparatus[1 110 11] are clearly indicative of its heightened state of activity As might be expected under such conditions these hypophyses reveal little storage of hormone when tested by implantation At the onset of pregnancy in the rat the acidophiles show degranulation numerous mitochondria and hypertrophy of the Golgi apparatus whereas the basophiles do not appear to be altered significantly Toward the middle of pregnancy however the basophiles become large and granular and during the latter third they show a considerable depletion of their specific granules and a marked increase in their eosin staining mitochondria The latter may be deceptive since it imparts to the basophile the appearance of an atypical bigranular cell[3] Kirkman[1] has reported that the pregnant guinea pig s hypophysis is characterized principally by mitochondria filled degranulated basophiles He observed also a significant increase in the number of acidophiles toward the end of pregnancy and in the post partum period The latter has been confirmed for the full term human hypophysis [8] and has been noted also in the rat [1]

Comte [5] was among the first to recognize a change in the human hypophysis during pregnancy In addition to the increase in size and weight of the gland to which Comte called attention Erdheim and Stumme[1] observed an acidophile like cell which they named the pregnancy cell Their statement that it originated from the chromophobe has been substantiated since then but their belief that it represented a new cell type has not been confirmed by subsequent investigators [3 80 11 114] The pregnancy cell has been described variously as a large finely granulated chromophobe or a small finely granulated acidophile These forms which apparently represent a different state of its activity indicate that it arises from a chromophobe which becomes granulated and degranulated in accordance with a well recognized cycle of secretory function

FIG 19 (1) Anestrous cat Low power view of mid portion of a frontal section of the adenohypophysis The central area (gray) of basophiles and chromophobes is the zona tuberalis which divides the adenohypophysis into right and left halves The majority of the cells in the latter are ordinary acidophiles (dark) (2) Anestrous cat Medium power view (frontal section) of area from one wing of pars distalis Ordinary acidophiles are dark and clusters of small chromophobes are gray (3) Cat 1 hr 40 min after mating Medium power view (frontal section) of a peripheral area adjacent to the zona tuberalis showing the characteristic alveolar pattern of the carmine cells (dark) Ordinary acidophiles are also present (gray) (4) Oil immersion view of deeper lying area from the same adenohypophysis as (3) showing the distinctly granulated carmine cells (dark) scattered among the more homogeneous ordinary acidophiles (gray) (Appropriate filters were used in each instance to achieve the desired contrast between the variously stained cells for purposes of photographic clarity) Reproduced from Endocrinology 1940 XXVI 20 2

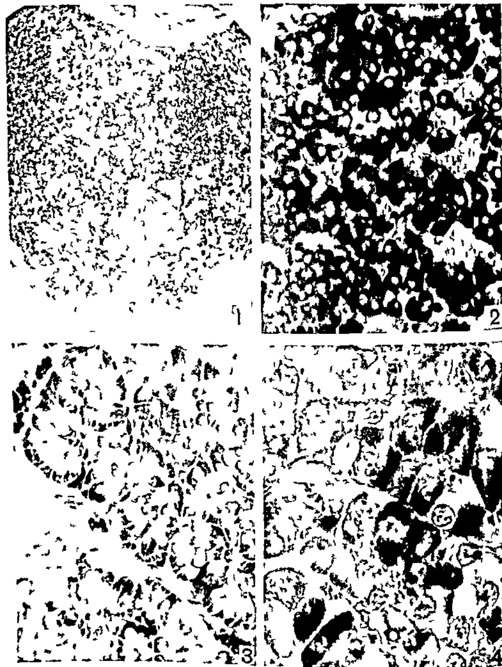


FIG 19 For legend see page 828 (41

decrease of the basal metabolic rate[129,13,133]. Appropriate replacement therapy obviates this evidence of functional deterioration[1,134].

Injections of acid or alkaline extracts of the adenohypophysis stimulate the functional activity of the normal thyroid gland by virtue of a thyrotropic hormone which has been isolated in highly purified form. Such extracts initiate metamorphosis in the larvae of axolotls, frogs and salamanders because of the hyperthyroidism which is induced by the thyrotropic hormone[35,136,137,13,39,14,141,14]. Injections of extracts containing thyrotropic hormone also bring about similar functional and histological changes in the thyroid glands of birds and mammals as follows:

(1) Parenchymal hypertrophy and hyperplasia of the thyroid gland with liquefaction and loss of colloid[1,116,143,14,146,147,1,149,1,151,15,54,1,5,156,15,158,159,1,0,1,16,161] all of which eventually recede in spite of continued injections of the extract[143,153,16,163] (Fig. 20).

(2) Hypertrophy of the Golgi apparatus and mitochondria of the thyroid gland[157].

(3) An initial increase in basal metabolic rate[154,16,163] which returns spontaneously to its normal level in spite of uninterrupted injections of the extract[16,16,163,16]. This rise in basal oxygen consumption can be prevented from the very beginning[15,166,167] or decreased after it has become elevated[166,167,168,60,1,0] by the administration of potassium iodide. The rise in basal metabolic rate after the administration of thyrotropic hormone is known to be directly dependent upon the presence of the thyroid gland and cannot be provoked in its absence[158,171]. In general, however, the increased basal metabolic rate, which is induced by a chemically crude adenohypophysial extract, is due only in part to thyroid stimulation. Another, more rapidly elicited increase in the rate of oxygen consumption has been noted in fed animals shortly after the injection of such extracts, and it is not prevented by thyroidectomy[1,173,174]. Riddle and his co-workers[173] believe that this calorigenic action is elicited in pigeons by prolactin.

(4) Decrease in total and protein bound iodin in the thyroid gland simultaneously with their increase in the blood stream[175,7,1,7,1,1,9].

(5) Exophthalmos in metamorphosing tadpoles[36,137,13] as well as in ducks and guinea pig[5,5,1,16,15] (Fig. 21). This exophthalmos can be produced in the absence of the thyroid gland[171,18].

(6) Tachycardia[15,16,87,143] and abnormal nervous irritability in guinea pigs[1,183].

The experimental syndrome induced by such adenohypophysial extracts shows certain interesting correlations between the structure and function of the thyroid gland[16]. The intraperitoneal administration to guinea pigs of an extract containing the thyrotropic hormone induces a rise in basal metabolic rate which be

The Thyrotropic Hormone

Chemistry

Janssen and Loeser[11] were among the first to purify the thyrotropic hormone substantially and subsequently Loeser[116] described a method of obtaining a highly active preparation of the thyrotropic hormone in stable dry form Various substances have been used in the extraction of this hormone, including aqueous solutions of pyridine[11, 11] diethylamine[116] ammonia[11, 118], dilute acetic acid[117] and flavianic acid[1 9] An extensive study of the purification of the thyrotropic hormone has been carried out recently by Jorgensen and Wade[1 1] and by Bonsnes and White[1] Starting with an extract prepared by Bonsnes and White[1], White and Ciereszko[1 1 1] studied further the fractionation and isolation of the thyrotropic hormone from beef hypophyses They developed a method which resulted in the preparation of a protein fraction high in thyrotropic hormone activity and homogenous in both the Tiselius apparatus and ultracentrifuge The final product of this procedure is a white powder readily soluble in water and precipitated from neutral solutions by the addition of acetone to a concentration of 75 per cent The preparation gives the usual qualitative protein color tests The labile sulfur and Molisch tests are positive Phosphorus is not present The protein is precipitated from aqueous solution by phosphotungstic acid, picric acid uranium acetate and mercuric chloride but it is not precipitated by sulfosalicylic acid or by lead acetate A total of one microgram of this material will produce a minimum histological response in the three day old chick if given once daily for 5 days This preparation has an approximate molecular weight of 10,000 Similar fractionation studies of sheep hypophyses indicate that the thyrotropic hormone fraction from this source in contrast to that obtained from beef hypophyses is not yet homogenous in the Tiselius apparatus[1 5] There are at least two protein components present in the most highly purified sheep thyrotropic fractions now available Bioassays of purified thyrotropic hormone prepared from beef and sheep indicate that the activity of the latter is approximately twice that of the former per unit of weight[1 5]

Physiology

Effects of Hypophysectomy or of Injection of Adenohypophysial Extracts on Structure and Function of Thyroid Gland — It is well established that the functional state of the thyroid gland can be influenced greatly by the adenohypophysis Ablation of the adenohypophysis causes a retardation of development or atrophy of the thyroid gland[1 6 1 7 1 1 9 130 131], as a result of which there is a significant

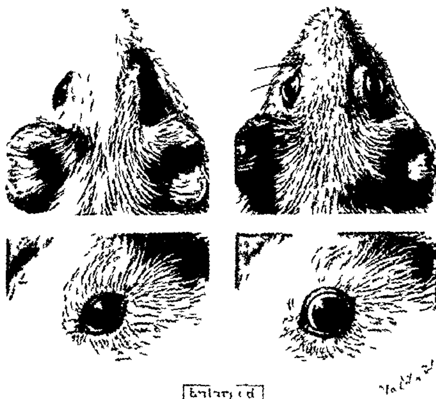


Fig 21 Upper and lower left Normal appearance of eyes in an untreated guinea pig as seen from above and laterally Upper and lower right Exophthalmos in guinea pig induced by daily intraperitoneal administration of an alkaline extract of the adeno hypophysis Reproduced from Bulletin of the Johns Hopkins Hospital 1934 LIV 48

gins within 18 hours and reaches its peak of 22 to 66 per cent about the seventh or eighth day of the experimental period Exophthalmos appears toward the end of the first week of treatment The thyroid gland shows hypertrophy and hyper plasia of the acinar epithelium and of the mitochondria The Golgi apparatus is hypertrophied The amount of acinar colloid diminishes as the total and protein bound iodin in the thyroid decreases and there is a parallel increase in the con centration of the iodids in the circulation The rise in basal metabolic rate the development of the hypertrophic and hyperplastic changes in the thyroid gland the increase in the concentration of iodin in the circulation and its decrease in the



Fig 20 Thyroid glands from guinea pigs Upper left untreated control Upper right injected daily with chemically crude adenohypophysial extract containing thyrotropic hormone B M R + 40 per cent autopsied on fifth day Lower left similar treatment for 10 days B M R + 100 per cent died of thyrotoxicosis on eleventh day Lower right similar treatment for 18 days B M R + 51 per cent on eleventh day + 25 per cent on eighteenth day when animal died of thyrotoxicosis Reproduced from Bulletin of the Johns Hopkins Hospital 1934 LIV 48

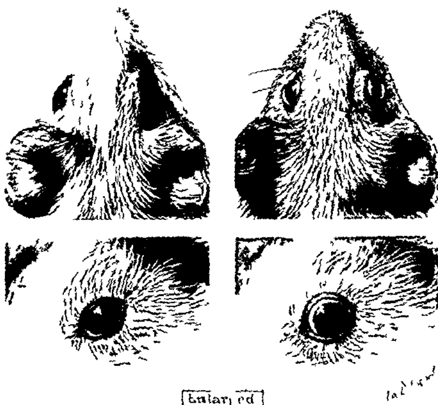


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gins within 18 hours and reaches its peak of 2 to 66 per cent about the seventh or eighth day of the experimental period Exophthalmos appears toward the end of the first week of treatment The thyroid gland shows hypertrophy and hyper plasia of the acinar epithelium and of the mitochondria The Golgi apparatus is hypertrophied The amount of acinar colloid diminishes as the total and protein bound iodin in the thyroid decreases and there is a parallel increase in the con centration of the iodids in the circulation The rise in basal metabolic rate the development of the hypertrophic and hyperplastic changes in the thyroid gland the increase in the concentration of iodin in the circulation and its decrease in the

thyroid gland take place coincidentally Within a week or 10 days a remission in the metabolic disturbance develops in spite of, and because of, the continued administration of the adenohypophysial extract which contains the thyrotropic hormone The immediate reason appears to be the inactivation of the thyrotropic hormone by the formation of an antibody to its protein content[163, 169, 1 4] The basal metabolic rate returns to its normal value within 1 to 3 weeks Sometimes, however the decreasing rate of oxygen consumption overshoots its original mark and descends to a hypothyroid level, probably because the thyroid has been emptied of its normal colloid stores Involution of the parenchymal hypertrophy and hyperplasia and reaccumulation of acinar colloid lag moderately behind the decreasing metabolic rate By the time the basal metabolic rate has reached its normal level however these regressive, histological changes are fairly complete, although the reaccumulated colloid is rather poor in iodin About 8 per cent of the guinea pigs studied were resistant to the thyrotropic effects of the extract and revealed a highly curtailed initial increase in the rate of metabolism and a strong tendency toward an early remission[163, 164] Occasionally a brief transitory secondary rise in the rate of metabolism occurred after such an abortive response On the contrary there are other guinea pigs, even less in number, which display only a negligible resistance to the extract, and after a rapid initial increase in the rate of oxygen consumption suffer several marked exacerbations of their hyperthyroidism Sex is one of the factors that plays a role in the variable response which the thyrotropic hormone elicits This is significant in view of its similar importance in the clinical syndrome of exophthalmic goiter Although not an invariable occurrence the metabolic disturbance is more intense and of longer duration in the female than in the male guinea pig[169, 170]

The metabolic effect of the adenohypophysial thyrotropic hormone is enhanced significantly if its daily administration to tadpoles or guinea pigs is combined with the injection of either adrenalin or pilocarpine[185, 186, 187] Friedgood Bevin and Uotila[186] have suggested that the pilocarpine may act through the adrenal medulla and that the adrenalin renders the thyroid cells more sensitive to the thyrotropic activity of the adenohypophysial extract Friedgood and Cannon[1 8] have demonstrated that the thyrotropic hormone does not affect the thyroid function by way of its cervical sympathetic innervation As a matter of fact recent evidence[169] is against the conception that the autonomic innervation of the thyroid gland activates the function of the parenchymal cells directly

Comparison of Experimental Adenohypophysial Hyperthyroid Syndrome with Exophthalmic Goiter in Man — Friedgood has demonstrated that the signs symptoms clinical course and response to iodin of the experimentally induced adenohypophysial hyperthyroidism are essentially identical with those encountered in human exophthalmic goiter[16, 163] With the exception of diffuse and

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nodular lymphoid hyperplasia which are absent in the thyroids of experimental *adenohypophysial hyperthyroidism the gland is identical in every respect with* that of exophthalmic goiter in man. The effect of iodin on the thyroid altered histologically by an adenohypophysial extract and upon the course of experimental adenohypophysial hyperthyroidism is exactly comparable in all known *respects to that of its action in exophthalmic goiter* [61, 1]. *The response of* the experimental hyperthyroid syndrome to a given dose of iodin ranges from one which is barely recognizable to one which completely obliterates the hyperthyroid state. Within the limits studied larger doses of iodin were more effective than smaller doses in preventing or partially interfering with the expected cycle of hyperthyroidism [61]. As in exophthalmic goiter an inadequate dosage of iodin occasionally induced an exacerbation of the hyperthyroid state whereas a large dose sometimes was followed by a decrease in metabolic rate to hypothyroid levels [67, 1, 9, 170].

It is recognized generally that in most cases of exophthalmic goiter treated with iodin there is an optimal period during which the basal metabolic rate decreases to its lowest level and after which it increases in spite of the continued administration of the drug. This has led to a widespread practice of restricting the use of iodids to the preoperative preparation for thyroidectomy during the second or third week of therapy. Escape from the depressant influence of iodin also occurs in experimental adenohypophysial hyperthyroidism. Means and Lerman[19] believe that the secondary increase in metabolism in the clinical syndrome is not dependent upon refractoriness to iodin but should be attributed to an increase in the intensity of hyperthyroidism which masks the effect of the iodin. The observed effect of iodin on the course of experimental adenohypophysial hyperthyroidism suggests another possible explanation for this phenomenon. This evidence indicates that the action of iodin is short lived in the experimental syndrome and it has been established by other adequate metabolic and cytological data that the effect of iodin on the thyroid is transitory or in other words that the thyroid becomes refractory to its action[189, 191, 1, 193, 94, 195, 196, 187, 188, 1, 9]. *Since the response to iodin in the experimental and clinical syndromes is identical in every other way* it is probable that the same is true of the post iodin or refractory phenomena. In this connection it should be emphasized that the administration of iodin is attended not only by a temporary depressant *effect upon the rate of secretion of the thyroid hormone but also by the rapid* restoration to the thyroid of a previously depleted store of hormone. This unusual accumulation of colloid makes it possible for the thyroid which is in a hypersecretory state to deliver increasing amounts of thyroid hormone to the circulation as soon as the depressant effects of iodin wear off. This accounts satisfactorily for the apparent increase in intensity of hyperthyroidism which

Means has noted In accord with this hypothesis is the observation that the administration of iodin sometimes causes an exacerbation instead of a depression of the hyperthyroidism both in the experimental and the clinical syndrome Analysis of the experimental data indicates that this occurs whenever the dosage of iodin is too small to be effective[169 1 0] A similar response has been noted *infrequently as a result of what appears to be an individual idiosyncrasy* of the animal In either of such circumstances the metabolic forces, which promote hypersecretion are greater than those which inhibit it *Consequently replenish*ment of the depleted colloid adds fuel to the fire of hyperthyroidism

The point at which iodin is administered in relation to the cycle of hyper thyroidism in the experimental syndrome influences to some extent the intensity of its effect If iodin is withheld until the 'spontaneous' remission begins, it induces a rapid decrease in the basal metabolic rate which persists for some time at a hypothyroid level[1 1] This finding may be of practical importance in *directing the therapy of those patients* with exophthalmic goiter, in whom the administration of iodin occasionally results in an unusually prolonged remission *at hypothyroid levels On the basis of these experimental results the* author suggested[1 9 1] that such patients might be entering upon a favorable phase of the malady and consequently would be more suitable for continued treatment with iodin than for thyroidectomy This has been confirmed by Means and Hertz[09]

Cytology in Relation to Secretion

The cytological changes, which occur in the hypophysis in both types of chromophiles after thyroidectomy are not unlike those following gonadectomy[6 01 0] There is a *marked increase in the number of basophiles*[6 39 0 0 04], which occurs within a week after thyroidectomy subsequent to which vacuola*tion becomes apparent The onset* of vacuolation is earlier and its speed and degree of development are much more pronounced after thyroidectomy than following castration In the early stages the cytological appearance of these vacuolated basophiles is remarkably similar to the typical castration cell[7 01] The older vacuolated 'thyroidectomy' basophiles become much larger and more irregular in outline than the 'castration cell

Experimental thyroidectomy in the rat and rabbit results in a marked decrease in the acidophiles of the hypophysis[6 01 3 04 0 06] Identical observations have been reported in clinical myxedema[0 0 08 09 10] The decreased proportion of acidophiles induced by *thyroidectomy apparently* is more pronounced than that which occurs following castration The marked loss of acidophiles is due to a permanent *depletion of their specific granulation* which reaches its peak after about 6 weeks At this time there may be no acidophiles,

all of the latter having returned to an inactive chromophobic state There is a *concomitant regression in the Golgi apparatus which retains its characteristic* acidophilic type [91] The administration of thyroid substance either parenterally or orally, to the thyroidectomized rat or rabbit specifically restores the acidophiles to their normal numbers [6, 96]

The parenteral or oral administration of thyroid to normal adult male rats results in an increase in the number and vacuolation of the basophiles [11] Curiously enough this vacuolation is identical with that found after castration or thyroidectomy The hyperthyroid rats also develop a marked acidophilia These cells are actively secretory the Golgi apparatus and mitochondria are hypertrophied, the cells grow larger and their granules which show a marked affinity for the dye are being discharged constantly

Although similar cytological changes occur in the basophiles after gonadectomy and thyroidectomy the hypophysis exhibits an increased gonad stimulating power after the former but not the latter *This suggests either that there is no* correlation between cytology and function or that what appear to be identical cytological changes represent closely allied biochemical processes which are engaged in the manufacture of different tropic hormones

The Ophthalmotropic Activity of the Adenohypophysis and its Bearing on the Clinical Syndrome of Exophthalmic Goiter

Introduction

The pathogenesis of exophthalmos in exophthalmic goiter has been the subject of considerable controversial speculation for a period of many years This situation may be attributed to the fact that opportunities for the experimental study of exophthalmos in the human are subject to obvious limitations Recent advances have made it possible however to induce exophthalmos experimentally in mammals and the results of such investigations have been found to be applicable to the problem in man A review of the clinically important aspects of this situation was undertaken by this writer in a previous communication[184] The present discussion is concerned only with the role of the adenohypophysis in the experimental production of exophthalmos and with the physiological and clinical significance of this relationship

Historical Consideration

In 19 4 Spaul[187, 188] noted that bulging of the eyeballs was one of the earliest manifestations of the metamorphosis induced in normal tadpoles and axolotls by

injections of a crude adenohypophysial extract Schockaert[153] was the first, however to comment specifically on the exophthalmos which results from such treatment The ducks with which he worked developed hyperthyroidism within the first week of the experiment and 14 out of 15 showed exophthalmos on or about the 20th day of injection The exophthalmos vanished promptly during ether anesthesia and disappeared within one or two weeks, if the injections were discontinued The following year[1] Loeb and Friedman issued a brief communication on studies of the guinea pig in confirmation of Schockaert's work They observed the appearance of exophthalmos after 4 to 6 daily injections of an acid extract of the adenohypophysis and found that it disappeared in complete narcosis, malnutrition and death Friedgood[16 163] noted similar decreases in exophthalmos very early in the experimental period but he reported that the position of the eyeball was not affected appreciably by narcosis or death once the exophthalmos was well established (see Fig 21)

Relation of Thyroid Function to Experimental and Clinical Exophthalmos

Friedgood[163] has made detailed observations on the intensity of exophthalmos in relation to the state of function of the thyroid gland in guinea pigs injected daily for 6 months with a potent chemically crude adenohypophysial extract He found that the hyperthyroidism induced by daily injections of an alkaline adenohypophysial extract lasts about 2 to 3 weeks after which the basal metabolic rate falls to a slightly subnormal level in spite of continued injections of the extract Exophthalmos appeared in 9 out of 30 treated guinea pigs during the height of the hyperthyroidism but it became more marked when the hyperthyroidism declined and was most striking when the basal metabolic rate became abnormally low

It was concluded that a decrease in function of the thyroid favored the development and persistence of the exophthalmos which resulted from daily injections of this adenohypophysial extract As a matter of fact the entire absence of thyroid function makes the action of extracts provoking exophthalmos even more effective because exophthalmos appears more promptly and more frequently in thyroidectomized guinea pigs than in normal ones[171 182]

It is agreed generally that exophthalmos in exophthalmic goiter is not due to the hyperthyroidism per se and that exophthalmos cannot be induced by the administration of thyroid to a normal animal Moreover it is commonly recognized that exophthalmos is not necessarily present even in severe cases of exophthalmic goiter Exophthalmos frequently may appear for the first time after subtotal thyroidectomy for exophthalmic goiter or, having been present before

operation can become worse afterwards Ruedemann [1] who has made an extensive study of exophthalmos in post operative exophthalmic goiter, attributes its development to a deficient thyroid secretion which is characterized in most cases by a progressive lowering of the basal metabolic rate In a case of this sort he found edema of the upper and lower eyelids and a classical picture of post operative myxedema

That myxedema can in some circumstances either be responsible for or favor the development of exophthalmos is well known Cley [3] was the first to report that thyroidectomized rabbits might develop myxedema spontaneously and Marine and Rosen [14] have found that thyroidectomized rabbits are much more likely to develop exophthalmos induced by cyanide than are unoperated controls Rabbits are highly sensitive subjects for this experiment but the condition apparently also occurs with some rarity in the myxedema of man (see unpublished data of Friedgood Cattell and Beetham[1])

Thomas and Woods [15] studied 15 cases of progressive exophthalmos following thyroidectomy in man In those orbits which were explored they found Tenon s capsule displaced anteriorly by edematous hypertrophied retrobulbar tissue On the basis of their experience these investigators conclude that exophthalmos may develop in the absence of clinical hyperthyroidism but they do not consider that hypothyroidism is an essential predisposing factor In an effort to justify their belief that thyroid insufficiency is not an important factor in the pathogenesis of post thyroidectomy exophthalmos they point out that total ablation of the thyroid in the treatment of cardiac failure does not induce exophthalmos

They overlooked the fact, however that the fundamental pathological physiology prior to operation differs completely in both instances In the case of the cardiacs the function of the endocrines prior to thyroidectomy has been essentially unaffected in that of the goiter patients there already existed a stimulus which is potentially or actually productive of exophthalmos It is true that thyroidectomy in exophthalmic goiter generally affects this stimulus favorably by interrupting whatever it is that initiates the entire goiter syndrome but in the light of other well known evidence it appears likely that in a small percentage of cases a serious form of exophthalmos may be precipitated by this operation The protective action of an intact thyroid function against the development of exophthalmos is substantiated further by Soley s experiments [16] He found that there was an increase in prominence of the eyes of a majority of the patients with toxic diffuse or toxic nodular goiter following subtotal ablation of the thyroid although clinically the eyes appeared less prominent The apparent improvement of the exophthalmos was due mainly to disappearance of the staring expression which results from retraction of the upper lids

mos persisted unabated The changes in the orbit apparently were reversible early in this syndrome but became irreversible eventually Aird [19] who confirmed and extended these observations, found that the pathological anatomy of the orbital tissues and extraocular muscles in the irreversible phase of the guinea pig s exophthalmos is identical with that which Naffziger [0 1] and others had described for the orbital contents in patients with post operative malignant exophthalmos Smelser [ ], who also has confirmed the author s observations of chronic adenohypophysial exophthalmos, investigated the retrobulbar tissue changes responsible for the proptosis His pathological studies showed that the same retrobulbar tissue changes occurred in the exophthalmos of man and of thyroidectomized guinea pigs injected with an adenohypophysial extract The exophthalmos was due to increased amounts of orbital tissue, such as fat, connective tissue and muscles and there was a great deal of edema of these retrobulbar tissues

Less lymphocytic infiltration and involvement of the extraocular muscles were found in guinea pigs than in man Paulson [4], who studied this problem also, was impressed with the marked edema which he found in the extra ocular muscles retrobulbar fat and loose connective tissue This evidence as a whole links an important aspect of Graves' disease securely to its counterpart in the experimental animal syndrome

One may assume for the present until further evidence is brought to bear upon the problem, that ordinary exophthalmos in exophthalmic goiter and so called malignant exophthalmos represent reversible and irreversible phases, respectively, of this phenomenon In such circumstances a single stimulus could be responsible for the development of both types of exophthalmos the so called malignant type would occur clinically only when certain conditions favored the onset of the irreversible phase The intensity of the stimulus producing exophthalmos must be one of these conditioning factors, and another is apparently a decrease in function of the thyroid gland There are probably a number of other factors which play an important role in this connection The sex of the individual and the state of function of the gonads probably are among those which significantly influence the stimulus producing exophthalmos

Hertz Williams and Means [18] have pointed out that malignant post operative exophthalmos is much more common in males than in females Marine [5], who reviewed 52 such cases in the literature up to 1936 found that the group consisted of 31 males, 60 per cent and 21 females 40 per cent respectively It is an interesting coincidence that Marine s experimental studies of methyl cyanide exophthalmos in rabbits have yielded a similar correlation between that type of exophthalmos and sexuality of the animal Cyanide exophthalmos develops most frequently in young sexually active, male rabbits and is greatly amelio

rated or prevented from developing by performing gonadectomy [14]

Judging from the clinical course of both types of exophthalmo reversible and irreversible the changes in the orbital tissues which are responsible for protrusion of the eyeballs must be in part of a labile nature The prominence of proptosis in acute exophthalmic goiter may fluctuate quite readily from time to time and exophthalmos sometimes recedes fairly rapidly in a post thyroidectomy remission Moreover the development of malignant post operative exophthalmos frequently is of strikingly sudden onset and rapid progression There is no acceptable evidence upon which to postulate that the muscles of the orbit take a significant part mechanically in pulling the eyeball forward[1 *] Nor is it conceivable on the basis of this evidence that engorgement of the blood vessels per se could account for this condition although this factor has not been studied exhaustively as yet Careful tudies of the orbital contents of patients dying with acute exophthalmic goiter show surprisingly little Friedenwald [6] found the extraocular muscles of 6 such patients entirely normal and those in a seventh case were slightly enlarged and showed degenerative changes and cellular infiltration On the other hand striking pathological changes have been noted in the extraocular muscles and orbital tissues of patients with post thyroidectomy exophthalmos [0 1 27 8 9 0]

The sum total of these and other observations indicate that three pathological changes are characteristic of so called malignant post thyroidectomy exophthalmos (1) marked enlargement of the extraocular muscles associated with edema lymphocytic infiltration and fragmentation of muscle fiber (2) edema of the orbital fat and connective tissue (3) increase in the amount of fat and retrobulbar connective ti ue which with the exception of the edema appear to be normal histologically

The encroachment of these space-occupying pathological changes on the contents of the non distensible orbital cavity adequately accounts for the progressive and serious nature of such proptosis Available evidence suggests that this is the human counterpart of the irreversible phase of exophthalmos which was observed in the guinea pig syndrome Analysis of the foregoing pathology discloses that only one of the three changes mentioned could possibly be reversible viz the edematous condition of the orbital tissues Can it be that a disturbance in water balance leading to edema of the orbital tissues is the immediate cause of exophthalmos in acute exophthalmic goiter? This would account for the essentially negative post mortem findings in the orbits of many such patients and fits in with the edema or puffiness of the eyelids which is seen not uncommonly in exophthalmic goiter (Figs 2 and 23) Whether or not the irreversible pathological changes are merely secondary to damage done by edematous infiltration of the retrobulbar tissues is a problem for further study This is not quite likely since the marked

increase in the fat and connective tissue content of the orbit is also in need of explanation

The effect of the ophthalmotropic substance, which produces exophthalmos particularly in post operative malignant cases, is especially noteworthy because of its predilection for the orbital tissues, although patients thus afflicted often show



FIG 22 Persistent severe exophthalmos after subtotal thyroidectomy which alleviated clinical syndrome otherwise Note edema of the upper and lower eyelids with only slight widening of the palpebral fissures

evidence of edema elsewhere, e g pitting edema over the tibiae This is apparently not the only substance which acts thus since para phenylenediamin hydrochloride exhibits a similar property and likewise induces exophthalmos the anatomical cause of which is edema of the orbital tissue [31] This chemical, which thus affects dogs and monkeys, also causes increased epiphora chemosis and injection of the conjunctivae findings which closely parallel the eyes signs in malignant, post thyroidectomy exophthalmos

The use of the word ophthalmotropic with reference to this effect of an adenohypophysial extract does not imply that a specific chemical substance having this physiological action is believed to exist as such in the gland The fact that the ophthalmotropic activity of the extract probably is directly or indirectly responsible for the edema of the orbital tissues suggests that it may be tied in



Fig 23 Persistent mild exophthalmos after subtotal thyroidectomy Note marked edema of eyelids particularly the upper The exophthalmos appears to be more prominent than it actually is because of the strikingly widened palpebral fissures Compare with Fig 22 *in which the situation is quite the reverse Reproduced through the courtesy of the Department of Surgery* Peter Bent Brigham Hospital

with the important role which the adenohypophysis plays in regulating water metabolism That this may be a generalized disturbance in water metabolism is suggested by two other observations (1) the edema in patients of this type may be particularly impressive in the orbit but it has been observed also in other tissues e g over the tibiae (2) an impaired function of the thyroid gland apparently is a common finding in this type of patient How this contributes to the tendency to develop exophthalmos is unknown but it is well to recall that the thyroid influences water metabolism and may have an essential relation with the adenohypophysis in maintaining a proper water balance

Clinical Application of Experimental Observations on Ophthalmotropic Activity of Adenohypophysial Extracts

The observations which have been presented, indicate that exophthalmic goiter is a syndrome in which either the thyroid or the eyes may become the outstanding problem in therapy It is essential, therefore, to be able to differentiate clinically between these two types of cases, for in the one thyroidectomy is at present usually the treatment of choice, while in the other this operation may precipitate a disastrous ocular complication Our clinical experience still is too limited to speak with assurance of this differential diagnosis, but where so much is at stake in the choice of therapy, one is justified in being guided for the present by certain common sense, clinical criteria and by the experimental laboratory data

Since edema of the orbital tissues probably is an early pathological change in this type of case one should regard with suspicion any preoperative chemosis, lacrimation or puffiness and venous congestion of the eyelids The development of hypothyroidism during iodin therapy or the presence of thyrotropic hormone in the urine likewise should put one on guard, since these findings are associated with an abnormal decrease in thyroid function which undoubtedly is a predisposing factor in the development of ocular complications As a matter of fact a decrease in metabolic rate to hypothyroid levels during iodin therapy may be a contraindication to thyroidectomy even if exophthalmos is not the major consideration Haines [3] and Thompson and his associates [33, 34, 35] have described a group of patients with exophthalmic goiter, in whom the administration of iodin causes a significant fall in basal metabolic rate to what are ordinarily considered moderate hypothyroid levels seldom below minus 20 per cent The latter may occur with or without clinical evidence of hypofunction of the thyroid gland or myxedema The significance of this clinical observation became clear during a study of experimental adenohypophysial hyperthyroidism in guinea pigs treated with iodin[166, 167] and led the author to postulate that patients reacting in this manner to iodids were entering upon a favorable phase or remission of their malady and were more suitable for continued treatment with iodids rather than for thyroidectomy[169, 1 0, 184] Hertz and Means [0] subsequently found this to be a valuable guide in their selection of cases for non surgical treatment Finally one should hesitate to operate on individuals particularly males who have an exophthalmos which is a more striking part of the syndrome than their hyperthyroidism or thyroid enlargement (Fig 24)

The features which have been mentioned already, likewise should be warning signals in the post operative period An increase in exophthalmos, the development of edema or venous congestion of the eyelids and a relatively low basal

metabolic rate especially if associated with an increasing blood cholesterol or the appearance of thyrotropic hormone in the urine, may be significant premonitory findings

The medical treatment of post-operative malignant exophthalmos once it has developed, is notoriously unsatisfactory Dessicated thyroid, either alone or in combination with iodin, has had only meager success in our hands and apparently

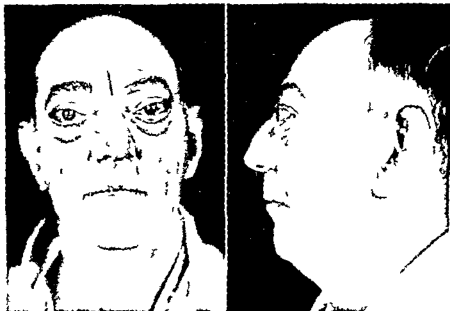


Fig 24 Post thyroidectomy malignant exophthalmos Note extensive edema of upper and lower eyelids chemosis and epiphora Patient treated with success subsequently by x ray therapy of the orbit

this is also the experience of others Presumably the administration of thyroid would be more effective as a preventive than as a therapeutic procedure once this difficulty has developed The administration of large doses of estrogenic hormone in an effort to depress the activity of the adenohypophysis in a case of menopausal hyperthyroidism has met with partial success in one patient (Fig 25) The right eye improved markedly but the increasing chemosis and progressive protrusion of the left eye which was involved more seriously failed to respond satisfactorily X ray therapy to the hypophysis was not tried in this case, because our limited experience with it at the Peter Bent Brigham Hospital has not been encouraging At the suggestion of Dr M C Sosman several advanced cases



FIG 25 Malignant post thyroidectomy exophthalmos which appeared for the first time after operation Right and left upper photographs taken before treatment show extensive exophthalmos chemosis epiphora and edema of eyelids Lower photograph shows results of therapy with estradiol dipropionate thyroid and application of x rays to orbit

in that clinic have been treated by irradiation directly to the orbit Thus far the results have been impressive but the series of cases is too small to warrant further comment The hope of developing an ideal treatment for this condition lies of course, in a thorough understanding of all the major factors which promote its development Until more is known of these, one should avoid thyroidectomy

in those cases which look suspicious preoperatively If one is confronted for one reason or another with the necessity of subjecting to operation a patient who falls into this category it would be a wise precaution to administer dessicated thyroid in addition to iodin preoperatively, in order to prevent the development of at least one condition viz hypothyroidism which is known to affect the eyes of such individuals adversely

The Carbohydrate Regulating Mechanism of the Adenohypophysis

Physiology

Clinical aspects — Clinical disorders of the adenohypophysis not infrequently are associated with disturbances in carbohydrate metabolism In the hyperfunctional phase of acromegaly for instance there may be a decreased tolerance for carbohydrates with hyperglycemia and glycosuria whereas in Simmonds disease and in the late stages of acromegaly the hypofunctional state of the adenohypophysis is characterized in part by chronic hypoglycemia and hypoglycemic crises There are differences likewise in the reaction of such patients to insulin Conditions which are induced experimentally to simulate these clinical syndromes have served admirably in the study of this endocrine phase of carbohydrate metabolism The latter is affected in essentially opposite directions by adenohypophysial deficiency due to hypophysectomy and by injections of adenohypophysial extracts which induce a functional state equivalent to adenohypophysial hyperactivity

Adenohypophysial Deficiency and Carbohydrate Metabolism — Hypophysectomy in the dog results among other thing in hypoglycemia [6 37] extraordinary sensitivity to insulin interference with gluconeogenesis from protein [1] and in fasting animals a rapid depletion of the glycogen stores of the liver and muscles [3 4] The effect of hypophysial ablation on carbohydrate metabolism has been illustrated in still another way by Houssay and Biasotti [1] who noted that the course of diabetes in pancreatectomized toads and dogs is ameliorated markedly by hypophysectomy inasmuch as such animals live longer show less glycosuria and have only infrequent acetonuria as compared with pancreatectomized controls The decrease in the rate of glucose absorption from the intestinal tract which is characteristic of the hypophysectomized rat [43 4] has been traced to the secondary hypothyroidism which occurs after hypophysial ablation

Excessive Adenohypophysial Secretion and Carbohydrate Metabolism — A functional state exactly opposite to that observed after hypophysectomy can be created by the administration to normal animals of a chemically crude adenohy

pophysial extract The extent of the effect of such extracts on carbohydrate metabolism and the direction which it takes often are determined by species susceptibility and the state of nutrition of the experimental animals Such extracts exhibit diabetogenic glycostatic glycotropic and ketogenic metabolic effects

THE DIABETOGENIC EFFECT — Glycosuria and hyperglycemia result from injections of such adenohypophysial extracts into animals on a normal diet [4, 47, 48] and a well established diabetic condition supervenes, if these injections are administered to susceptible animals, such as the dog over a prolonged period of time This diabetogenic action is less marked in other species, but the inability of the organism to utilize carbohydrates properly during injection of such extracts can be detected by a depression in the respiratory quotient and by characteristic alterations in the glucose tolerance curve [49]

THE GLYCOSTATIC EFFECT — Adenohypophysial extracts, which induce hyperglycemia in fed animals particularly dogs fed carbohydrates, are likely also to bring about an increased accumulation of muscle and liver glycogen This glycostatic effect of the extract quite obviously is the reverse of that which results from hypophysectomy In normal fasted rats however the injection of such extracts reduces protein catabolism which in turn induces hypoglycemia, because the amino acids are the only source of glucose in such circumstances [50]

THE GLYCOTROPIC EFFECT — By virtue of its glycotropic activity an adenohypophysial extract may either abolish the hypoglycemic effects of insulin in normal animals or at least increase resistance to the insulin effect This functional state is the opposite of that which follows hypophysectomy, since the latter renders an animal extremely sensitive to insulin

THE KETOGENIC EFFECT — In fasted susceptible animals adenohypophysial extracts generally produce a condition, which commonly complicates the course of diabetes mellitus in man viz an increased rate of fat catabolism with acetonemia and acetonuria [1, 5, 3, 4] Long [4] points out that this increase in fat catabolism probably compensates for the decrease in protein catabolism which results from treatment with the extract The latter implies that the organism must shift to some other foodstuff to replace the calories lost by the reduction in the proportion of protein in the metabolic mixture

EVIDENCE BEARING ON THE EXISTENCE OF A PANCREATOTROPIC HORMONE

General Considerations — There is considerable discussion in the literature concerning the evidence for and against an adenohypophysial pancreatotropic hormone Claims for the existence of such an entity are based principally on reports that the administration to animals of relatively crude adenohypophysial extracts induces an hypertrophy of the islands of Langerhans an increase in the

insulin content of the pancreas and a decrease in the blood sugar level in certain circumstances The available evidence on these points however is not clear cut possibly because of species differences and variations in the experimental conditions under which the extract is administered It must be emphasized moreover that the production of insulin and the oxidation and utilization of carbohydrates are only indirectly and probably not directly dependent on endocrine factors Thus the tissue demands of the organism expressed through the blood sugar level are thought to be the factors that regulate the production and supply of insulin This is not to deny that the endocrine glands play an important role in the acceleration or inhibition of certain phases of carbohydrate metabolism In this connection Long points out that although the absence of insulin leads to interference with the utilization of carbohydrates removal of the hypophysis or adrenal cortex restores to some degree the ability of the organism to oxidize carbohydrate foodstuff

Adenohypophysial Deficiency in Relation to Pancreatic Function and Morphology —Ablation of the adenohypophysis is followed ordinarily by atrophy and other evidence of hypofunction in the case of all target endocrine glands whose activity is controlled by an adenohypophysial tropic hormone Adenohypophysectomized animals however do not exhibit signs of insulin deficiency As was indicated above they actually show a tendency to utilize carbohydrates to an extraordinary degree Furthermore there is no clear-cut agreement on the morphological changes induced in the pancreas by hypophysectomy Koster [5] who found atrophy of the pancreas in the hypophysectomized dog suggested that the hypophysis might be instrumental in the maintenance of pancreatic function whereas von Bakay [6] reported that the islands of Langerhans were increased in size and number 2 to 6 months after hypophysectomy in the dog Perhaps the time factor is an important consideration in this question

Excessive Adenohypophysial Secretion in Relation to Pancreatic Morphology and Function — Anselmino and Hoffman [7] found that their adenohypophysial extracts which were reported to be free of thyrotropic and gonadotropic effects induced hypertrophy and hyperplasia of the pancreatic islets The decreased blood sugar level of their dogs treated with this extract suggested that the hyperplastic islet tissue also showed increased functional activity Richardson and Young likewise have noted islet hypertrophy in rats treated with crude adenohypophysial extracts which were known to produce glycosuria and permanent diabetes in dogs Richardson and Young [58] found furthermore that extracts of known diabetogenic properties caused hypertrophy and hyperplasia of the islet cells initially only to induce subsequent hydropic and hyalin degeneration of these structures in dogs rendered permanently diabetic by such injections

There is apparently a marked species difference in the functional response of

islet cells to the administration of an adenohypophysial extract which influences carbohydrate metabolism Such treatment in the dog causes a rapid and considerable decrease in the insulin content of the pancreas [60], whereas the same type of extract increases the insulin content of the rat s pancreas both in the intact [61] and the hypophysectomized animal [6 63] Certain evidence suggests that chemically crude extracts of the adenohypophysis can be fractionated into two parts, one of which increases, while the other decreases the insulin content of the rat's pancreas [64]

Experimental studies of the insulin content of the hypophysectomized rat s pancreas have yielded essentially negative results Haist [6] has demonstrated that hypophysectomy only slightly reduces the insulin content of the rat s pancreas, and that the feeding of fat causes a further decrease just as it does in the normal rat which has not been operated upon The reduced insulin content of rats fed a fat diet can be restored to normal both in hypophysectomized rats and those not operated upon by returning them to a mixed diet Evidently the insulin content of the islet tissue not only is relatively unaffected by adenohypophysectomy but also is able to respond in the usual fashion to alterations in the demands of tissue metabolism for insulin

Nitrogen Retention in Relation to Adenohypophysial pancreatic Function — Mirsky [66] has suggested that the nitrogen retaining effect of adenohypophysial extracts is due to stimulation of the pancreatic islets by a pancreatotropic hormone The resulting increased supply of insulin was thought by him to decrease deamination in the liver and to increase protein synthesis in the muscles Young [67] who likewise supports the thesis of a pancreatotropic hormone, found that puppies, in contrast to dogs do not develop glycosuria when treated with an adenohypophysial extract unless it is administered over a prolonged period of months

Such puppies treated with extract show nitrogen retention and a gain in weight which occurs in association with hypertrophy and hyperplasia of the islet tissue Presumably the latter secretes enough insulin to neutralize, at least temporarily the diabetogenic activity of the extract Young suggests that the adenohypophysis contains at least two principles affecting carbohydrates i e a pancreatotropic hormone that stimuates insulin secretion, which in turn increases nitrogen retention and causes a gain in weight and a diabetogenic hormone which either suppresses carbohydrate oxidation or increases carbohydrate formation Gaebler and Gailbraith [69] have pointed out that an increased insulin output may not be the immediate and only cause of the observed nitrogen retention after injections of an adenohypophysial extract although they concede that the presence of insulin may be an essential prerequisite for it

Relation of Adrenocortical Function to Adrenohypophysial Regulation of Carbohydrate Metabolism

A discussion of adenohypophysial function in relation to carbohydrate metabolism scarcely would be complete without reference to the adrenal cortex because a large part of the diabetogenic activity of the adenohypophysis is mediated by the latter. The evidence on this point is unequivocal. The diabetes of partially depancreatized rats is aggravated by adrenocortical hormones of the corticosterone type just as it is by adenohypophysial extracts and total pancreatic diabetes is ameliorated to the same degree by adrenalectomy and hypophysectomy.[9] Furthermore both hypophysectomy and adrenalectomy decrease significantly the rate of protein catabolism and gluconeogenesis under the stress of fasting, exposure to cold or low oxygen tension, pyrogenic agents and phloridzin or pancreatic diabetes, all of which normally would increase the rate of protein metabolism and gluconeogenesis.[4] The decreased rate of protein catabolism and gluconeogenesis resulting from hypophysectomy may be attributed to hypofunction of the adrenal cortex because the administration of adrenocorticotropic hormones completely obviates the profound hypoglycemia and depleted carbohydrate stores which would occur otherwise in the fasting hypophysectomized animal.[4] Another metabolic defect common to hypophysectomized and adrenalectomized animals is their extraordinary sensitivity to insulin. It is interesting furthermore that the anti-insulin effect of *adenohypophysial extracts, the so called glycotropic activity,* is paralleled by an identical action of cortical extracts, adrenal steroids of the corticosterone type and the adrenocorticotropic hormone.[9] Because of the latter Jensen and Grattan have suggested that the adenohypophysial glycotropic effect is obtained indirectly through hypersecretion of the corticosteroids which *in turn increase the available carbohydrate stores of the liver and the blood sugar* level.[89]

Although a significant portion of the diabetogenic activity of the adenohypophysis is mediated by the adrenal cortex there are also some important differences which indicate that not all of the disturbances in carbohydrate metabolism after hypophysectomy can be assigned to adrenocortical hypofunction. One such difference between these two types of endocrine deficiency is illustrated by the alterations in carbohydrate metabolism which occur with fasting after hypophysectomy and after adrenalectomy. Fasting induces hypoglycemia after both operations but the decrease in blood sugar level is more profound and develops more rapidly after hypophysectomy than after adrenalectomy. Moreover the glycogen content of the liver is reduced markedly after either operation but the adrenalectomized animals maintain their muscle glycogen stores fairly well whereas *they are depleted rapidly in* hypophysectomized animals. The latter

taken in conjunction with the excessive rate of carbohydrate utilization of hypophysectomized animals constitutes a very significant difference between the two types of endocrine deficiency according to Long[4] These two types of glandular deficiences differ also in the rate of their immediate post operative, nitrogen excretion The nitrogen output proceeds at a greatly increased pace subsequent to hypophysectomy in rats, whereas it is much smaller than normal after adrenalectomy[4]

The adrenal cortex also initiates some direct effects of its own on carbohydrate metabolism Ingle has induced an extensive glycosuria in a normal rat injected daily with 11 dehydro 17 hydroxycorticosterone[7] Injections of such hormones do not alter the muscle glycogen of fasting animals, but they do increase markedly the glycogen content of the liver and raise the blood sugar level moderately Long[4] believes that the corticosterone type of hormone stimulates glucogenesis from protein directly and indirectly induces an increase in the rate of protein catabolism Long Katzin and Fry[71] have reported that this increased rate of protein metabolism which occurs concomitantly with the increase in carbohydrate stores of the organism is sufficient in magnitude to account for the extra carbohydrate found

The Adrenocorticotropic Hormone

Chemistry

Collip, Anderson and Thompson were the first to report the preparation of an adrenocorticotropic hormone by methods[7 3] which have not yielded successful results in other laboratories[1 5 74] The reasons for this failure to confirm Collip s work have been discussed at some length in a timely critique by White[1 5] Highly purified preparations of this hormone became available in 1933, and more recently these have been prepared without appreciable growth, gonadotropic or thyrotropic effects[1 74 75 6 77 8 9] Two groups of investigators, one at Yale[78 279], the other at California[77 80], have studied this problem independently with hog and sheep hypophyses respectively The adrenocorticotropic hormone content of the hog hypophysis is much higher than that of any other species examined[6 77 8] Although the methods of preparation used in the two laboratories are distinctly different one employing essentially salt fractionation[7] and the other isoelectric precipitation[279] it is clear that they have both succeeded in isolating the same substance from their two sources of supply Li, Simpson and Evans[280] have reported that their final product behaves as a single homogenous protein in electrophoretic and solubility studies Sedimentation and diffusion measurements also indicate that this preparation is homogenous or very nearly so Biological tests show that their adrenocorticotropic hormone is free of the other

adenohypophysial hormones The molecular weight was found to be approximately 20 000 and the isoelectric point about pH 4 7 The hormone is remarkably stable at 100 C in buffer at pH 7 5 and in 0 1 molar hydrochloric acid solution but not in 0 1 molar sodium hydroxide solution Although its biological activity is destroyed by trichloracetic acid and by tryptic digestion pepsin leaves it relatively unchanged

The purified adrenocorticotropic hormone prepared by the Yale group [8, 79] gives the usual protein color reaction The Molisch test is negative Although the labile sulfur test is positive the nitroprusside reaction for free sulfhydryl groups is negative The hormone is precipitated easily from dilute solution by 20 per cent sulfosalicylic acid by 20 per cent trichloracetic acid and by 5 per cent lead acetate solution The initial protein boundary was found to migrate as a single component at all pH values studied in the Tiselius apparatus i e pH 3 26 4 13 6 37 and 7 95 In accord with Li Simpson and Evans it is reported by White[125] that the molecular weight of the adrenocorticotropic hormone is 20 000 and the isoelectric point 4 7 to 4 8 Having subjected the purified adrenocorticotropic hormone to elemental analysis both groups of investigators report essentially the same percentage of carbon hydrogen nitrogen and sulfur

Physiology

Evidence for the existence of an adrenocorticotropic hormone like that for all other physiologically active substances of the adenohypophysis has been obtained from two general sources viz the condition of the adrenal gland after hypophysectomy and after the injection into animals of chemically crude and highly purified adenohypophysial extracts

Histological Changes in Adrenal Cortex Resulting from Hypophysectomy — It is accepted generally that hypophysectomy is followed by marked atrophy of the adrenal cortex in all species which have been examined [5] [3, 64, 68, 66] [7, 8, 6] and that compensatory adrenal hypertrophy which ordinarily follows unilateral adrenalectomy does not occur in the hypophysectomized animal [93] [8, 4, 5, 8] The histological changes in the adrenals of hypophysectomized rats and dogs have been investigated carefully [87] The medulla appears normal The cells of all three zones of the cortex are smaller but are not decreased in number Fat deposits are limited to a central zone The earliest changes appear in the reticular zone and in the inner part of the fascicular zone Here the cells become progressively smaller until these regions no longer possess a normal, cord like arrangement of cells Thereafter the entire cortex becomes involved similarly Evidence from clinical sources also amply confirms the dependence of the adrenal cortex upon intact adenohypophysial function Extensive atrophy of the

adrenal cortex is associated with adenohypophysial pathology and hypofunction [98, 99] In hypophysial dwarfism the adrenals are very small and show hypoplastic changes in the cortical layers [00, 301, 30, 303] In Simmonds' cachexia the adrenal glands are small although frequently histologically normal[304, 30, 306, 307]

Histological Changes in Adrenal Cortex Induced by Adenohypophysial Extracts — In 1929 Putnam Benedict and Teel[308] found cortical adenomas in the adrenals of dogs, which were injected over a relatively long interval with an alkaline extract of the adenohypophysis In 1932 Evans and associates[309] observed that the injection of growth promoting extracts caused cellular hypertrophy of the fasciculate zone with some increase in the amount of cortical lipoids In 1933 Emery and Atwell [6], Friedgood[16, 163, 310] and Houssay and associates [83] reported independently that the daily injection of partially purified adenohypophysial extracts resulted in marked hypertrophy and hyperplasia of the adrenal cortex in the rat, guinea pig and dog This was confirmed abundantly by numerous subsequent observers, some of whom demonstrated also that suitable extracts or implants of the adenohypophysis restored the atrophied adrenals of hypophysectomized animals to their preoperative normal state Emery and Atwell concluded that the hyperplastic changes in animals treated with adenohypophysial extract involved both reticulate and fasciculate zones[28]

Early studies seemed to show that this adrenocorticotropic effect of the adenohypophysis was mediated through the thyroid gland[311, 31, 313, 314, 315] In a statistical analysis of his data Friedgood[310] demonstrated, however, that only a portion of the adrenocortical hypertrophy could be attributed to the thyroid hormone He based this conclusion on the fact that the significant correlation between adrenal weights and intensity of hyperthyroidism accounted for merely a part of the adrenocorticotropic effect of the adenohypophysial extract This was confirmed subsequently by others who found that adrenal hypertrophy occurs in thyroidectomized animals treated with adenohypophysial extract[310, 317, 18]

Functional Significance of Histological Alterations — The functional significance of these histological changes is far from being understood, but a good beginning has been made in its investigation Among the physiological effects, which have been observed after the administration of the adrenocorticotropic hormone are alterations in the cholesterol and ascorbic acid content of the adrenal cortex, changes in the structure and function of lymphoid tissue and inhibiting influences on body weight chondrogenesis and osteogenesis The relation of this hormone to renal hypertension, work performance and carbohydrate metabolism also are being investigated

Cholesterol and Ascorbic Acid Content of Adrenal Gland — In view of the fact that the active principles of the adrenal cortex are steroids, the cholesterol content of the gland has been investigated with the thought that variations in its

concentration might reflect changes in the synthesis and secretion of the steroid hormones Such studies have disclosed that a single dose of adrenocorticotropic *hormone diminishes the cholesterol content of the adrenal cortex of the immature* white rat by one half to two thirds of its normal level within 3 hours whereas repeated daily injections over a period of 3 days results in an increase of the cholesterol content above the normal control level[319 3 0 3 1] The initial maximum depletion of cholesterol which takes place 3 hours after the administration of hormone is followed by recovery within 12 to 24 hours Sayers Sayers Lewis and Long[3] have postulated that the more rapid depletion and recovery in the ascorbic acid content of the adrenal cortex after similar hormone therapy is related either *to the synthesis of adrenocortical hormone or its release from the adrenal gland*

Influence on Structure and Function of Lymphoid Tissue and Spleen — In 1936 Perla[a 3 3] and Friedgood[1] called attention independently to the possi*ble significance of certain relations between the adenohypophysis and the spleen* The author[319] reported that a statistically significant increase in the weight of the spleen of guinea pigs resulted from the daily injection of an alkaline extract of the pars distalis of the adenohypophysis He observed furthermore that the splenomegaly occurred in association with marked hypertrophy of the adrenal cortex A limited cycle of hyperthyroidism due to hypertrophy and hyperplasia of the thyroid parenchyma represented another coincidental change induced by the adenohypophysial extract The mean weight of the spleens removed from normal *females was found to be significantly greater than that of the spleens from normal* males In this connection it may be of interest to point out that the female hypophysis is heavier on the average that that of the male in all human races which have been studied The pioneer and important investigations of Perla[3 a] extended and interpreted these observations in the relation of the spleen and adenohypophysis from an immunological viewpoint His data proved that hypophysectomy is followed by a decrease in natural resistance to various toxins and poisons and to spontaneous and induced bacterial and protozoal infections be*cause of atrophy of the spleen and lymphoid tissue of the body* *Perla demon*strated moreover that the adenohypophysis affects the animal s natural resistance because of the controlling influence of the adrenocorticotropic hormone over the physiological activity *of the adrenal cortex and the spleen and lymphoid* tissues The more recent investigations of Dougherty White and Chase[3 3 4 3] have confirmed and extended the foregoing observations with a pure adrenocorticotropic hormone They have found that the adrenocorticotropic hormone and the adrenocortical steroids are concerned with the mechanism of antibody *formation from lymphocytes It is proposed to discuss certain aspects of this* immunological problem since it is germaine to any consideration of adenohypophysial function

adrenal cortex is associated with adenohypophysial pathology and hypofunction[298, 299] In hypophysial dwarfism the adrenals are very small and show hypoplastic changes in the cortical layers[300, 301, 302, 303] In Simmonds' cachexia the adrenal glands are small although frequently histologically normal[304, 305, 306, 307]

Histological Changes in Adrenal Cortex Induced by Adenohypophysial Extracts —In 1929 Putnam Benedict and Teel[308] found cortical adenomas in the adrenals of dogs, which were injected over a relatively long interval with an alkaline extract of the adenohypophysis In 1932 Evans and associates[309] observed that the injection of growth promoting extracts caused cellular hypertrophy of the fasciculate zone with some increase in the amount of cortical lipoids In 1933 Emery and Atwell , Friedgood[162, 163, 310] and Houssay and associates[88] reported independently that the daily injection of partially purified adenohypophysial extracts resulted in marked hypertrophy and hyperplasia of the adrenal cortex in the rat, guinea pig and dog This was confirmed abundantly by numerous subsequent observers, some of whom demonstrated also that suitable extracts or implants of the adenohypophysis restored the atrophied adrenals of hypophysectomized animals to their preoperative normal state Emery and Atwell concluded that the hyperplastic changes in animals treated with adenohypophysial extract involved both reticulate and fasciculate zones[8]

Early studies seemed to show that this adrenocorticotropic effect of the adenohypophysis was mediated through the thyroid gland[311, 312, 313, 314, 315] In a statistical analysis of his data Friedgood[310] demonstrated, however, that only a portion of the adrenocortical hypertrophy could be attributed to the thyroid hormone He based this conclusion on the fact that the significant correlation between adrenal weights and intensity of hyperthyroidism accounted for merely a part of the adrenocorticotropic effect of the adenohypophysial extract This was confirmed subsequently by others, who found that adrenal hypertrophy occurs in thyroidectomized animals treated with adenohypophysial extract[316, 317, 318]

Functional Significance of Histological Alterations —The functional significance of these histological changes is far from being understood, but a good beginning has been made in its investigation Among the physiological effects, which have been observed after the administration of the adrenocorticotropic hormone, are alterations in the cholesterol and ascorbic acid content of the adrenal cortex, changes in the structure and function of lymphoid tissue and inhibiting influences on body weight chondrogenesis and osteogenesis The relation of this hormone to renal hypertension, work performance and carbohydrate metabolism also are being investigated

Cholesterol and Ascorbic Acid Content of Adrenal Gland —In view of the fact that the active principles of the adrenal cortex are steroids, the cholesterol content of the gland has been investigated with the thought that variations in its

in antibody titer in the serum was observed to parallel the activity of the lymphoid cells of the Malpighian bodies of the spleen

This circumstantial evidence was reinforced conclusively by the observations of McMaster and Hudack[3] who showed that antibodies may be formed in lymph nodes When they injected two different antigens into a mouse one into each ear the corresponding antibody appeared first in the ipsilateral lymph node Ehrich and Harris[3] demonstrated subsequently that the cellular response during antibody formation in such lymph nodes is lymphocytic essentially Further observations revealed that the injection of antigens into the pad of the hind foot of a rabbit was followed within 2 to 4 days by the appearance of antibodies in the lymph draining the corresponding popliteal lymph node The antibody titer was higher in the lymph of the efferent vessel by as much as 100 times that found in the lymph of the afferent vessel The production of antibody in the popliteal lymph node was preceded by and associated with a four fold increase in the output of lymphocytes in the efferent lymph At the same time the hyperplasia of the lymphatic tissue within the lymph node resulted in an increase of 0 2 gm to 1 0 gm in the weight of the latter In a more recent communication Harris Grimm Mertens and Ehrich[3] reported that during antibody formation in the popliteal lymph node of rabbits the lymphocytes in the efferent lymph vessels contain antibodies in a much higher concentration than the surrounding lymph Ehrich and Harris believe that the evidence[3 34 3] is entirely against the possibility that the lymphocyte either absorbs or adsorbs these antibodies it favors the lymphocytic theory of antibody formation Many clinical and patholgical observations support this viewpoint[33 333 33]

The mechanism of antibody formation like all other physiological processes is subject to regulation and control under normal circumstances The recent investigations by Dougherty White and Chase[3 4 5 3] have been instrumental in disclosing one of the ways in which this functional adjustment may be accomplished Moreover their studies give experimental support to the clinical belief that the adenohypophysis has something to do with the regulation of the number of circulating leucocytes and erythrocytes They found that the administration to mice and rats of pure adrenocorticotropic hormone resulted in a statistically significant decrease in the total weight of the lymphoid tissue exclusive of the spleen as compared with normal controls The weights of the inguinal axillary and mesenteric lymph nodes and the thymus were approximately one half that of the control animals[3 4 3 7] Further studies with mice and rabbits showed that within 3 hours of its injection this hormone induced degenerative changes in the lymphocytes of the germinal centers of lymph nodes in the Malpighian follicles of the spleen in the cortex of the thymus and in Peyer s patches The degenerative changes were characterized by pyknosis and nuclear fragmentation in the

The site of the formation of antibodies was conceded to be the reticuloendothelium until very recently although an increasing body of evidence, which had been largely ignored pointed to the lymphocyte as their source Metschnikoff s reticulo endothelial theory was accorded general acceptance, because it seemed plausible to believe that the cells, which phagocytize and destroy bacteria, should be concerned also with the synthesis of antibodies Of the various arguments, which were advanced in support of this theory, two have been favored e pecially One of these was based on the observation that the formation of antibodies may be depressed by blocking the reticulo endothelial system with phagocytized sub stances such as india ink trypan blue, collargol and iron sugar The second of these arguments in favor of Metschnikoff s theory was proposed by Sabin[3 5] She observed that the phagocytosis of a dye protein by a macrophage resulted in the removal of some of the dye from each dye protein aggregate With the removal of the dye the protein particles became invisible and antibodies made their ap pearance in the serum These phenomena were believed to signify that the protein was converted into a soluble form and assimilated subsequently into the cytoplasm The fact that the cytoplasm of the macrophage was shed coinci dentally with the disappearance into the cytoplasm of the dye protein aggregate and the appearance in the serum of antibodies seemed to indicate that the anti body was synthesized within the cytoplasm of the macrophage and extruded sub sequently into the circulating blood Ehrich and Harris[3 9], who have reviewed the experimental data critically have come to the conclusion that the interpreta tion put upon them is open to question They believe, on the contrary, that the known facts are consistent only with the lymphocytic theory of antibody for mation

Among the first to contribute to the long chain of evidence in favor of the lymphocytic origin of antibodies was Hektoen[11] who showed that the exposure of rats to x ray caused a decrease in the production of hemolysin coincidentally with a reduction in the number of circulating lymphocytes and in the mass of lymphatic and bone marrow tissue Murphy and Sturm[131] reported subsequently that similar treatment which affected the lymphatic tissue without damaging the bone marrow induced definite decreases in the production of precipitins bacterial agglutinins and protective antibodies in rabbits They noted furthermore that exposure of rabbits to dry heat caused an increase in the activity of the lymphatic tissue which was paralleled by the development of larger quantities of antibodies than untreated animals were capable of producing Ehrich and Voigt[33] added to this evidence by showing that the antibody titer remained low after doses of staphylococcus vaccine which were large enough to stimulate marked prolifera tion of the reticuloendothelium whereas high titers were elicited with small doses, which did not produce visible proliferation of these cells Furthermore, the rise

mone to the action of the growth hormone was noted also in its effects on the osseus system of normal and hypophysectomized rats[3 344] The proximal epiphyses of the tibiae in normal animals showed retardation in chondrogenesis and osteogenesis but the reduction in width of the epiphyseal cartilage was not so extensive as that which develops after hypophysectomy These bone changes did not occur in the absence of the adrenal glands In hypophysectomized rats highly purified growth hormone induced activation of the cartilage of the proximal epiphyseal regions of the tibiae and formation of the delicate, straight trabeculae of bone was resumed The adrenocorticotropic hormone scarcely affected the inactive condition of the epiphyses on the other hand except that the cartilage cells in the erosion zone were more irregular

Relation to Renal Hypertension Work Performance and Insulin Content of Pancreas — A group of interesting experiments have been reported by Anderson Page Li and Ogden[4] on the restoration of renal hypertension in hypophysectomized rats by the administration of adrenocorticotropic hormone They found that hypophysectomy was followed originally by an average decrease of 44 mm Hg in mean blood pressure The significance of these findings is far reaching inasmuch as they indicate that the adenohypophysis and the adrenal cortex play an important role in the regulation of the renal factors which are responsible for the development of this type of hypertension

Ingle Li and Evans[3 5] have investigated the effect of pure adrenocorticotropic hormone on the work performance of hypophysectomized rats They observed that the hormone induced a marked increase in the amount of work elicited from the gastrocnemius muscle of such animals as compared with the very poor work performance of untreated rats Moreover they noted that repetitive direct faradic stimulation of these muscles resulted in a loss of responsiveness within 12 to 18 hours in the untreated animals whereas the muscle responsiveness lasted 24 to 120 hours in the rats that received the adrenocorticotropic hormone The metabolic importance of these findings is self evident but their ultimate significance still is to be explained

In a previous section of this chapter there appeared a detailed account of the functional relations which exist between the adenohypophysis and the adrenal cortex in so far as carbohydrate metabolism is concerned The availability of a pure adrenocorticotropic hormone with which to experiment has helped to reconcile some of the results of investigators who worked previously with chemically crude adenohypophysial extracts For instance the recent observations of Fraenkel Conrat Herring Simpson and Evans[344] may have a bearing on the question of a pancreatotropic hormone inasmuch as they found that the adrenocorticotropic hormone increased the insulin content of the rat s pancreas by an average of 40 per cent above the normal level The physiological significance

small and medium sized lymphocytes After 3 to 6 hours the lymphoid tissue showed a marked depletion of lymphocytes associated with extensive edema Restoration of the normal structure of lymphoid tissue began about 9 hours after an injection and was detectable for as long as 24 hours subsequently None of these structural changes occurred in adrenalectomized animals which were injected with the same hormone

The loss of lymphocytes from lymphoid tissue was found to be associated with a marked decrease in the number of cells in the circulating blood Single injections of the adrenocorticotropic hormone into mice, rats rabbits and men resulted in a decrease in the total leucocyte count a decrease in the absolute number of lymphocytes and an increase in the absolute number of polymorphonuclear neutrophiles There was also an early initial increase in the amount of hemoglobin, the number of lymphocytes in the circulating blood and probably, the number long as 24 hours afterward The lymphopenia may be considered a specific response to the adrenocorticotropic hormone because it does not occur in adrenalectomized animals treated with this hormone or in normal animals injected with a pure protein Lymphopenia is induced in intact and adrenalectomized animals, however, after injection with extracts of the adrenal cortex, adrenocortical steroids in oil corticosterone or Wintersteiner s compound F Desoxycorticosterone was not found to affect the total number of blood lymphocytes in normal or operated animals On the basis of these studies Dougherty and White[3 7] concluded that the number of lymphocytes in the circulating blood and probably the number of erythrocytes is under the control of the adenohypophysis by way of the adrenal cortex

Coincidentally with the involution of lymphoid tissue and the occurrence of lymphopenia there is a significant increase in the total serum proteins as a result of the administration of adrenocorticotropic hormone[3 5] White and Dougherty[3 5] suggest that a portion of this protein may undergo gluconeogenesis in the liver, another portion apparently augments the globulin fraction of the serum proteins, inasmuch as the antibody titer is increased in such circumstances[3 6] These observations tie in neatly with the array of evidence which was cited above, in favor of the lymphocytic origin of antibodies The inauguration of this metabolic phase of immunology may well be the beginning of a new approach to the clinical handling and therapeutic control of certain types of infection

Inhibiting Effect on Body Weight Chondrogenesis and Osteogenesis — Evans Simpson and Li[340] have demonstrated that the body growth of normal and gonadectomized male rats is inhibited by pure adrenocorticotropic hormone derived from the hypophyses of sheep This inhibitory effect was not observed in rats after adrenalectomy which indicated that the phenomenon was mediated by the adrenal cortex The antagonism of the adrenocorticotropic hor

acidophiles are concerned principally with adrenocortical function were it not for studies which have disclosed that the basophiles are the cells that are affected principally in the adenohypophyses of Addison's disease Kraus [6, 50, 51], who examined 7 cases of Addison's disease with tuberculous lesions of the adrenal and 2 other cases of adrenocortical atrophy with the classical Addisonian symptoms reported a general marked diminution in the number of normal basophiles There was almost complete absence of the basophiles in one instance only a slightly decreased number of basophiles in another and a marked decrease in their number in the remaining cases In only one instance was there sparse granulations of the basophiles in the others the basophiles appeared degenerated with indistinct and irregular cell borders degranulation and pyknotic nuclei The acidophiles also were affected somewhat similarly, viz diminished in number atrophic and with pyknotic nuclei The chromophobes consequently were present in larger than normal numbers although many of those were smaller than normal and had pyknotic nuclei These observations were confirmed subsequently in a statistically significant study by Crooke and Russell[35] of 12 similar cases Berblinger[353, 3, 4] studied 4 cases of which one showed no change in the adenohypophysis and another disclosed only a slight diminution in the basophile count whereas there was a very marked decrease in the basophiles in the remaining 2 cases He regarded the alterations in basophiles as the characteristic adenohypophysial finding in Addison's disease Terplan and Sanes [55] reported a case of Addison's disease treated with adrenal extract in which the hypophysis showed dilation of the capillaries a decreased number of basophiles and a normal chromophobe and acidophile count although the latter were slightly atrophic The basophiles showed degenerative changes characterized by indistinct cell outlines and small eccentric pyknotic nuclei Harrop Weinstein and Marlow[3, 6] have reported a decreased basophile count in association with atrophy of the adrenal cortex Only one case of Addison's disease has been reported in which the basophiles were found to be increased in number and in which there was cytological evidence of a heightened secretory activity of these chromophiles[7]

Whereas there is general accord in the reports on adenohypophysial cytology in Addison's disease the literature dealing with histological changes after experimental adrenalectomy in animals is confusing and contradictory [57, 35, 3, 380] Schumacker and Firor [9] examined the hypophysis of a bilaterally adrenalectomized dog that had been maintained in a state of chronic adrenal insufficiency for 128 days after operation They found conditions strikingly like those reported for Addison's disease viz increased vascularity of the hypophysis and a complete disappearance of the basophiles

In attempting to arrive at an understanding of the effect of adrenalectomy on the adenohypophysis there is one factor peculiar to adrenal function which must

of these experiments still remains to be determined, because an increase in the hormone content of an endocrine gland does not signify necessarily that it is associated with hypersecretion For example, the thyroglobulin content of the thyroid gland in exophthalmic goiter is at a remarkably low level at a time when its rate of secretion is augmented greatly Consequently their observations are not incompatible with those of Ingle ', who reported that the normal rat reacts to the daily injection of 11 dehydro 17 hydroxycorticosterone with hyperglycemia and glycosuria This is true particularly, if one assumes with Long ' that the corticosterone type of hormone stimulates gluconeogenesis from protein directly The extra carbohydrate formed in this fashion, furthermore might be protected by the glycotropic or anti insulin effect, which has been attributed to the adrenocorticotropic hormone by Jensen and Grattan [cv] Their findings are in accord with the undue sensitivity to insulin, which characterizes what may be considered the opposite functional state viz hypofunction of the adrenal cortex or Addison s disease

Bio assay

Simpson Evans and Li[345] have proposed two methods for the standardization of the adrenocorticotropic hormone The first unit is based on the daily dose in mgm , which is necessary to maintain the preoperative adrenal weight for 15 days in male rats that were hypophysectomized at 40 days of age The second unit is determined on female rats that are 26 to 28 days old at the time of hypophysectomy and 40 to 42 days of age when a 4 day period of injection with the test doses of hormone is begun The unit is based on the total dose in mgm which induces evidence of adrenal repair i e redistribution of cortical lipid, during the 4 days of administration of the hormone

Cytology in Relation to Secretion

Current thought on the cytological origin of the adrenocorticotropic hormone has been based chiefly on studies of the adenohypophysis in Addison s disease and in adrenalectomized animals The bearing on this problem of the cytological changes characteristic of the adenohypophysis of the acromegalic have been ignored essentially Some of this evidence is contradictory at least on superficial examination, much of it has not been interpreted physiologically as yet Hyperplasia of the adrenal cortex is the rule in acromegaly This disorder is characterized by acidophilic hyperplasia or adenoma with concomitant functional hyperactivity Although hyperplasia of the adrenal cortex is the usual finding [98 346 347 348 349] not infrequently adenomata of the cortex also enlarge the adrenals to a marked degree[2 8 348 349] These findings might suggest that the

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In attempting to arrive at an understanding of the effect of adrenalectomy on the adenohypophysis there is one factor peculiar to adrenal function which must

be taken into consideration. The removal of any endocrine gland induces serious disturbances in all metabolism, but the adrenal differs from all other glands in that its bilateral removal or pathological destruction results in death to the entire organism whose metabolic functions cannot proceed without its secretions. Consequently, the cytological appearance and functional activity of the adenohypophysial chromophiles must be affected in at least two ways by total adrenalectomy. There should be a specific local effect on the cells supplying the tropic hormone or hormones which are concerned with adrenal functions, and a non specific general effect on cellular metabolism. The adenohypophysial cells thus share in the serious consequences to the entire organism of the lack of the adrenal secretions. The latter probably accounts for the failure of the adenohypophysis to react to the insult of adrenalectomy by that pattern of response which characteristically occurs after ablation of certain of the other endocrine glands. For example thyroidectomy[361] gonadectomy[4, 3, 6, 34] and splenectomy[63] result, among other things in hypertrophy of the adenohypophysis with cytological and physiological evidence of hyperactivity either in the formation and storage or in the formation and secretion of the corresponding tropic principle. The rare instances in which cytological evidence of functional activity has been detected in the adenohypophysis of Addison's disease, probably resulted from abortive attempts at regeneration of the afflicted adrenal cells.

Further evidence bearing on the cytological origin of the adrenocorticotropic hormone has been reported by Koneff[364], who found that its administration to young and adult male rats results in a marked decrease in the size of the adenohypophysial basophiles and in an extensive depletion of their granules. Koneff believed these cytological changes to be indicative of a state of depressed or retarded functional activity. This response to the injection of the adrenocorticotropic hormone is in accord with the general physiological principle that the administration of a hormone is likely to be associated with involution of the cell which produces it in normal circumstances. The atrophic condition of the parenchyma of the thyroid gland which results from the ingestion of thyroglobulin, is encountered more commonly as an example of this principle. In the case of the thyroid gland the atrophy is secondary to a decreased rate of secretion of the adenohypophysial thyrotropic hormone resulting from an overabundance of circulating thyroglobulin. In like manner an overabundance of circulating corticosteroids, which are produced by the adrenal cortex in response to the adrenocorticotropic hormone, result in depression of the functional activity of the adenohypophysial basophiles. Thus a homeostatic mechanism regulates the rate of secretion of the thyrotropic and adrenocorticotropic hormones and others which behave similarly. This mechanism responds sensitively to the concentration in the blood of the hormone secreted by the target gland which has been stimulated

This ingenious manner of regulating the secretion of hormones is particularly effective because it becomes activated by the same physiological process it is supposed to prevent namely hypersecretion of a hormone Endocrine homeo tasis is achieved also through other physiological means at the disposal of the organism among which are the hypothalamus and the central nervous system Further discussion of this phase of the problem is being reserved for another chapter which is devoted to the endocrine functions of the hypothalamus Other a pects of the neurohumoral regulation of secretion have been described in Part V, which is concerned with the neurohypophysis

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PART III

BIOLOGICAL, BIOCHEMICAL, PHYSIOLOGICAL AND GENETIC CONCEPTS OF GROWTH

DEFINITION AND GENERAL CONSIDERATIONS

The inherent tendency to grow is one of the fundamental characteristics of living things. When used in a limited clinical sense, growth is a term which signifies an increase in the size of individuals with special reference to their height and weight. Growth may be regarded also as a fundamental biological property of the tissues and organs of physiologically young organisms which have not yet attained maturity. In this sense growth is the result of hypertrophy and hyperplasia of the cells of a tissue, organ or more substantial part of the immature individual. A continuation of the growth phenomenon likewise may be characteristic of certain tissues of a physiologically mature organism. For example the bone marrow continues to exhibit hematopoietic activity as long as the individual lives, although the bone itself ostensibly ceases to grow with the closure of the epiphyses. The products of hematopoiesis, primitive cells of the myelocytic and erythrocytic series, go through various recognizable phases of growth before arriving at maturity. From a biochemical viewpoint true growth is characterized essentially by an increased rate of protein synthesis, and the newly formed protoplasm, which represents the gain in weight, is known to be of rather constant composition[1-4]. The chemical characteristics of newly formed protoplasm, like immature tissue, include a relatively high content of water, protein and ash and a low content of fat.

The chemical composition of the organism differs at various stages of maturity. The intrauterine organism is composed of a relatively high proportion of water, 90 per cent, whereas the amounts of protein, 5 to 9 per cent, ash and fat, 1 to 2 per cent each are relatively small. After birth the proportion of protein which contributes to the gain in weight increases to approximately 15 to 20 per cent while that of water decreases commensurately. As the organism grows older, increasing quantities of fat are acquired, and since fat is deposited with relatively small quantities of water, the percentage content of the organism in water decreases still further. The amount of stored fat is fairly constant in young animals

but may vary within extremely wide limits among adults protein, on the other hand exhibits a very limited capacity for storage Because the continued acquisition of fat by the mature organism obscures the actual chemical composition of the body tissues during various stages of growth, Moulton[1] has calculated both the composition of the whole animal and the composition of the gain in weight on a fat free basis This analysis has revealed that the proportions of protein and mineral salts increase progressively during intrauterine life and for a brief period after birth Subsequent to this a point is reached after which the proportions of protein mineral salts and water remain remarkably constant although a highly variable amount of fat may be acquired Moulton has termed this constant period the 'age of chemical maturity'

That the chemical composition of protoplasm is in a constant state of dynamic equilibrium may be surmised from the fact that it is undergoing constant synthesis breakdown and resynthesis although its total quantity remains constant in the mature organism[5] The mature individual apparently retains and continues in operation those processes by which protein is formed and incorporated into protoplasm during the rapid growth period of the immature organism In the immature state these chemical processes result in a progressive increase in the bulk of living protoplasm, because protein synthesis is greater than protein catabolism in the mature state these processes are subjected to new forces which equilibrate the anabolic and catabolic phases of protein metabolism Some conception of the precision of this regulatory mechanism in the adult organism may be gleaned from the homeostasis of the blood proteins[6] the constancy of the nitrogenous constituents of the body and the narrow limits within which the chemical and metabolic characteristics of growth operate The growth phenomenon as a whole is under the control of biologically determined regulatory influences which limit the size of the organism or any of its parts to that destined for the species of which it is a member

The Rhythmic Progress of Normal Growth in Children

The rate of growth of normal children is characterized by a wide range of individual variations Although average standard growth curves have been constructed statistically on the basis of the general population one cannot apply them too specifically in individual instances Nevertheless such data have served a useful purpose in that they have drawn attention to the rhythmic pattern in which normal growth takes place The study of an average growth curve discloses faster and slower periods of growth which alternate in a fairly consistent fashion Godin[7] was among the first to point out that the growth of the long bones of the extremities proceeds by alternate periods of activity and repose which succeed each other

with regularity These alternate phases are not timed concurrently for the various long bones, e g the femur remains stationary during the period when the tibia grows and vice versa Godin found furthermore, that the resting period, during which there is no elongation, is utilized for an increase in the weight and thickness of the bone and vice versa Elongation of the long bones and increases in their transverse diameters and weights also were found to occur alternately, not simultaneously Godin concluded that growth prior to puberty is essentially osseous, while during puberty it is muscular Robertson[8] refers to three waves of growth, each of which is characterized by a period of gradual acceleration, then a peak and finally a phase of retardation The first wave occurs in the first year of post natal life the second phase of relatively rapid growth has its peak during the sixth or seventh years at the time of the second dentition, and the third spurt coincides with the onset of puberty The observations of Stratz[9] and Harris[10], like those of Godin indicate that skeletal growth periodically precedes muscular and visceral growth since they write of three "springing up" periods, each of which is followed by a 'filling out' period The cycles in their curves correspond chronologically with those of Robertson's[8] It is a matter of clinical record that disturbances of growth are most likely to arise during the three main "springing up periods i e during the first year of life, at the time of the second dentition and with the onset of puberty

A study of average normal growth curves discloses that certain variations can be attributed to sex differences The fast growing period in girls starts sooner finishes earlier and is less intensive than in boys Girls grow more steadily until puberty after which they are more likely to slow down, whereas boys often continue to grow rapidly throughout their early adolescent years Longitudinal growth ceases with the advent of sexual maturity because of closure of the epiphyseal junctions

Factors Affecting Growth

It is well established that growth is affected significantly by many extrinsic as well as intrinsic factors Among the former one may include deficiencies of diet disease and abnormalities of environment such as climatic, seasonal and hygienic conditions Of primary importance among the intrinsic factors are heredity and the growth regulating influences of the adenohypophysis, the thyroid, the adrenals the pancreas and the gonads

Diet

Nutritional deficiencies which affect growth most commonly, can be traced to the omission from the diet of certain indispensable vitamins to the inadequate

quality and quantity of the so called essential amino acids or to an insufficient total caloric intake The influence on growth of these various dietary factors may be studied in detail in the writings of Hopkins [?] Mellanby[1] McCollum and Simmonds[13] and Hess and in the reports of the Scottish Board of Health by Orr Leighton and Clark[15 16]

The short stature of the Italian of the Japane e and of certain other foreign nationalities has been attributed generally to hereditary influence but McCol lum[16] Manny [?] and Holt [8] have interpreted the situation otherwise Their data and that of others indicate that the optimal somatic growth of these peoples is limited significantly by diets which are inadequate in es ential proteins vitamins and minerals Osborne and Mendel[17] have demonstrated what striking varia tions there are in the value of proteins from different sources in so far as the sup port of growth is concerned They found also that animals remained stunted in growth for long periods when the protein content of the diet was limited in amount It is of interest from a therapeutic viewpoint that interruption of growth in such circumstances did not signify necessarily that the capacity to grow had been lost because an increase in the amount of protein of the diet caused the rats to resume growth at a predictable normal rate Mendel and Cannon found moreover that the albino rat has a more rapid rate of growth than that claimed to be standard for it by Donaldson in 1912 This change in the growth rate has been attributed not to selective breeding but to the feeding of a more appropriate diet than had been employed hitherto in the experimental study of rats McCol lum noted somewhat similar differences in the growth of his experimental rats When the nutrition of these animals fell just below a certain standard there was no recognizable sign of malnutrition but their size diminished from generation to generation The somatic inferiority of successive generations seemed to be the result of injury during the nursing period or might have been due to restricting the young after they were weaned to the same inferior diet as that of the parents The increase in size of Japanese children born in Californi where they are fed adequately over that of children of the same ages in Japan harmonizes with this viewpoint

Disease

Any extensive interference with nutrition from acute infections or metabolic disease results in limitation of the growth of the skeleton Harris[10] recently has observed that in such circumstances the structure of the bone is altered histo logically and roentgenologically by a transverse line of arrested growth Ap parently the growth cartilages cease to proliferate and become heavily calcified This line appears as a scar in the bone when growth is resumed Harris states

that such lines differ histologically only in extent from the lines of complete cessation of growth which result from final calcification of the epiphyseal junction Premature complete ossification of the growth cartilages, resulting in dwarfism, has been known to occur in children, who have suffered during the second decade from a series of severe infections, particularly the exanthemata

Heredity

It is a matter of common observation that heredity exerts an important effect on the growth of individuals This hereditarial influence has been associated by some authorities with the endocrine make up of the individual Although endocrine constitution is determined for the most part by heredity there are apparently other factors which affect the growth tendencies of the living organism A number of investigators among them Harrison[1], have demonstrated in their experimental work on the transplantation of limbs that these and other structures from two different sized species grow differently according to an individual capacity determined genetically in spite of an identical endocrine environment

The Endocrine Glands

The Adenohypophysis

The regulation of body growth and size is to a large extent, dependent upon the adenohypophysis This concept took form over a number of years as the result of clinical and pathological observations in giantism acromegaly and dwarfism in addition to physiological and biochemical studies of adenohypophysial function Among the outstanding contributions to this field have been the observations of Evans and Long and Stockard[3] The former demonstrated that daily long continued intraperitoneal injections of an adenohypophysial extract induced giantism in rats The growth curves of these experimental animals showed a steady continuance of growth as compared with the plateau of growth ordinarily encountered in untreated normal controls which reach adulthood These giant rats were proportioned symmetrically and weighed double that of their litter mates Roentgenological study of the giant skeletons disclosed that the normal size was exceeded by one and one half times Stockard s contributions, which were based on an extensive and fruitful experience are concerned with the constitutional and genetic aspects of the growth problem His concepts of the nature of growth are discussed in another connection in this chapter

Available evidence indicate that the adenohypophysis induces its effects by regulating growth largely through direct action on the tissues of the organism

but it also affects growth to some extent indirectly through the thyroid the gonads the pancreas and the adrenals which are under its physiological jurisdiction The fact that the function of the adenohypophysis is in turn subject to regulation by these and other glands of internal secretion complicates the problems of growth beyond our present ability to understand them completely

Experimental laboratory studies in this field apparently began in 1909 with Aschner s demonstration [4] that ablation of the dog s hypophysis results in dwarfism His observations were fully confirmed and extended subsequently by Smith [6, 7] and Allen who worked with tadpoles and rats and by Crowe, Cushing and Homans[1] and Benedict and Thomas [1] who experimented with dogs Similar findings for other vertebrates including primates have appeared since then in the literature along with improvements in as well as new procedures for the technic of hypophysectomy [3, 33, 34, 3]

The age of the animal at the time of hypophysectomy determines to some *extent the effect of this operation on growth and body weight Hypophysectomy* of immature rats 50 grams or less or of young rats before reaching their growth plateaux 80 to 120 grams results in the loss of only a small proportion of their original weight immature rats may even regain or exceed their preoperative weight level before growth stasis becomes complete Complete hypophysectomy in adult or almost full grown rats results in prompt cessation of skeletal growth which is due to failure of development of the cartilage cells in the epiphyseal discs[37] In addition there is a significant loss of body weight which is fairly rapid during the first few days after operation after which it becomes perceptibly slower until a level is reached some 20 to 40 per cent below the weight before operation[3, 33, 3, 38, 39] The loss in weight of the visceral organs is relatively greater than that of the other soft tissues These data obviously have an important bearing on the type of clinical disorders which may be expected from serious interference with or complete destruction of adenohypophysial function by pathological processes For instance complete ablation of adenohypophysial function in infancy or childhood ordinarily results in dwarfism uncomplicated by disorders of nutrition whereas similar pathology in the adult leads in certain circumstances to Simmonds cachexia

Disabilities resulting from hypophysectomy and their repair by appropriate replacement therapy have added further evidence to the many bonds linking the *adenohypophysis to body growth The administration of* adenohypophysial extracts containing the so called growth hormone or the implantation of fresh adenohypophysial substance induce a resumption of growth in the skeleton, the viscera and the other body tissues of hypophysectomized animals according to the observations of Smith[10] Reichert [1] Reichert Simpson Cornish and Evans[4] and Evans Pencharz Simpson and Meyer[43] In studies of this problem Thompson

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that true growth always is associated with the acquisition of body protein, tha changes in protein metabolism may be regarded as an accurate index to an im portant aspect of the growth process and that the adenohypophysis influences growth by virtue of its effect on protein metabolism

The injection of adenohypophysial extracts rich in growth promoting activity is accompanied by striking changes in protein metabolism A single injection significantly reduces the blood non protein nitrogen urea and amino acids in dogs and fasted rats[6 69] and causes a marked decrease in the excretion of urinary nitrogen in normal [1] and phloridzinized dogs [3] and in fasted rats[6] The decrease in the blood level of non protein nitrogen urea and amino acids occurs within a few hours of hormone administration and may persist for some time[69] Schaffer and Lee[7 3] have found that such injections cause a small decrease in the amino acids and urea content of the carcass and a much greater fall particularly of urea in the liver Prolonged treatment keeps these liver constituents at consistently low levels Other investigations of the chemical composition of animals which have been stimulated to an increased growth rate by these extracts show that the proportions of water protein and mineral salts in the gained weight reverts to that of the extra uterine type characteristic of normal rapidly growing animals Con sequently this gain in weight represents true growth The weight of evidence indicates that the growth hormone causes either an increased synthesis of protein or decreases the normal rate of protein catabolism Lee believes that the anabolic action of the growth hormone is first to conserve and increase the so called de posit reserve or storage protein and to decrease the exogenous catabolism of amino acids This stored protein probably is then incorporated into the less labile structural protein of the body by a process which may or may not be affected specifically by the growth hormone

The reverse of this metabolic picture is to be found in the hypophysectomized animal Perla and Sandberg[74] found an increased excretion of urinary nitrogen in hypophysectomized rats whereas young growing animals are always in po itive nitrogen balance So far as fat metabolism is concerned changes in the body composition of operated rats indicate that there is relatively little demand on stored fat for energy purposes whereas protein reserves are primarily mobilized and consumed[3] The normal rat on a restricted diet which is comparable to that voluntarily taken by a hypophysectomized animal utilizes fat stores for energy body protein being spared[3] The injection of growth hormone converts this metabolic picture to that of the actively growing young animal The foregoing data on fat catabolism dovetail neatly with the observation that the energy re quirements of the rat during the administration of a growth promoting adenohy pophysial extract is satisfied largely by the fat stores and that body protein is stored[4]

ing from insulin administration is principally responsible for the gain in weight which is observed after insulin therapy Insulin, however, has other physiological effects, which contribute at least as much, or even more, to its clinical usefulness in malnutrition It promotes the utilization of available stores of glycogen for energy, aids in the storage of liver glycogen induces nitrogen retention and plays an important role in the conversion of carbohydrates to fat[64 6] It is probable that these effects play a more important role than the increase in appetite in so far as the clinical usefulness of insulin administration in malnutrition is concerned

The Gonads

The growth response to injections of an adenohypophysial extract is not modified appreciably by the absence of the gonads[4], although the state of function of the gonads significantly influences the rate of growth In the human precocious puberty is associated clinically with dwarfism due to premature ossification of the epiphyses whereas a form of giantism in which the epiphyses remain ununited, is induced by castration or the occurrence of eunuchoidism before maturity[66 67 68] A more detailed discussion of gonadal influence on growth is to be found in a subsequent part of this chapter

Summary —The available evidence thus indicates that the thyroid adrenal cortex pancreas and gonads can modify the growth process to a striking degree that the growth promoting or nitrogen retaining properties of the adenohypophysis are not mediated through these glands and that the secretions of these four glands are essential to the optimal growth promoting function of the adenohypophysis One may infer from the foregoing data and conclusions that these various hormones possibly in definite proportions to each other, occupy a crucial position in a complicated well integrated series of chemical reactions, which are concerned with the metabolism and more specifically, the growth of protoplasm

The Metabolic and Physiological Effects of Adenohypophysial Extracts

On Protein and Fat Metabolism

Growth is a biological phenomenon characterized by a complex group of biochemical reactions which result in the synthesis of essential protoplasmic constituents and their incorporation into an integrated functional unit the cell Little is known of the mechanism by means of which these are accomplished, but certain aspects of it particularly in relation to adenohypophysial function, are coming rapidly to light It is clear from that which has been recounted already

tion against the expected thyroid atrophy Perla[81] subsequently confirmed the foregoing observations of splenomegaly in animals treated with adenohypophysial extract and observed also that hypophysectomy in rats is followed by a progressive atrophy of the spleen which is repaired by adequate replacement therapy

The fact that the liver of an animal treated with adenohypophysial extract enlarges out of proportion to the rest of the viscera or the body may be of special significance inasmuch as the liver is concerned with the most important aspects of protein metabolism Deamination of amino acids is dependent upon the presence of the liver which is also the most important if not the only site of urea formation in mammals Furthermore the blood protein fibrinogen is synthesized only in the liver [3]

The enlarged livers of those animals which were treated with such extracts retain the normal architecture of this organ and neither the hepatic cells nor their nuclei differ in size from those in normal control animals These findings taken in conjunction with the fact that the number of liver cells per gram of tissue remains unchanged [5] indicate that true hyperplasia has been induced by the adenohypophysial extract Since similar results have been obtained with purified thyrotropic hormone and thyroid hormone it is probable that the adenohypophysial growth factor is not primarily responsible for the hepatic hyperplasia[86]

On Skeletal and Integumentary Tissues

The skeletal deformities and skin changes which are among the salient findings in human gigantism and acromegaly find their counterpart in the experimental syndrome induced by adenohypophysial extract The acromegalic bull dogs prepared by Putnam Benedict and Teel [2] exhibited the extraordinary soft tissue hypertrophy and marked thickening and local deformities of the long bones which are characteristic of human acromegaly In less constitutionally predisposed dogs such as shepherds Evans and his coworkers noted thickening and enlargement of the skull bones without appreciable change in the long bones The achondroplasic short extremities of the dachshund were unaffected by extract therapy

Mortimer s[87] studies of the skulls of hypophysectomized rats and of rats treated with adenohypophysial extracts are of special interest to the clinician in view of the skeletal abnormalities which characterize the disordered growth in acromegaly gigantism and dwarfism Hypophysectomy results in skull changes which are more marked the earlier in life the gland is removed In very young animals the skull continues to increase in size slowly and in a modified manner since growth does not cease entirely because of the inherent capacity of young tissues to grow even in the absence of the adenohypophysis[87] The cranium grows

On Special Organs Other than the Endocrine Glands

Highly purified adenohypophysial extracts of the growth hormone were not available for experimental use until relatively recently Consequently most reported observations have been made with relatively crude extracts of this gland The interpretation of the results of these experiments is difficult in view of the characteristic secondary tropic effects which in turn induce widespread metabolic changes Nevertheless the results of such experiments closely parallel the pathological and clinical findings in giantism and acromegaly, possibly because the disordered adenohypophysial function in these diseases yields a secretion, which is comparable to that of the chemically crude extracts in experimental use The effects of these extracts in experimental animals have been particularly striking in the case of the visceral organs and skeletal system

On Visceral Organs

Putnam Benedict and Teel[51] observed a remarkable splanchnomegaly in a dog made acromegalic by treatment with such an extract The body weight of the animal at autopsy was 1 87 times that of its control litter mate sister The ratios of the weight of its visceral organs to those of the control were increased proportionately more with the exception of the spleen viz liver 3 42 lungs 3 36 pancreas 2 67 kidneys 2 43 heart 2 23 and spleen 1 16 There was also some increase in the connective tissues content of all the organs in the treated animal The adrenals contained cortical adenomas and the renal glomeruli and tubules were markedly hypertrophied The subcutaneous and omental fat deposits were notable for their paucity Downs [5] and Friedgood [6] also noted a disproportionate increase in the size of the liver in mice and guinea pigs respectively after treatment with adenohypophysial extract These investigators found a central necrosis in the livers of these animals Friedgood reported later [7, 8, 9] that marked enlargement of the adrenals due to cortical hypertrophy resulted from daily injections of an alkaline extract of the adenohypophysis This statistical study also disclosed that splenomegaly was an obvious but less consistent, feature of the experimental sydrome The splenomegaly was encountered far more frequently among the male than the female animals although the mean weight of the normal female spleen was found to be significantly greater than that of the normal male spleen There was no evidence that hypertrophy of these organs was related to the concurrent hyperthyroidism evoked by the extract This conclusion was substantiated by Collip Anderson and Thompson[80] who showed that the adrenocortical atrophy resulting from hypophysectomy can be obviated completely by daily injections of an adenohypophysial extract which is without similar protec

of endocrine dysfunction, in whom the histology of the adenohypophysis is fairly normal There are many breeds of dogs however, which are characterized by *peculiarities of type and distortions of form and growth which closely resemble* certain pathological conditions found in human families e g achondroplasia *dystrophia fetalis, giantism and hypophysial dwarfism* These structural ab normalities are associated with pronounced histopathological changes in the adenohypophysis which in ordinary circumstances might be held responsible for them

These various considerations led Stockard to make observations on the genetic developmental, anatomical and physiological characteristics of several highly modified dog breeds bred selectively over innumerable generations in order to perpetuate for dog fanciers reproducible types of localized skeletal deformities and generalized disorders of growth

A study of the development and adult condition of the bulldog s skull the bassethound s fore and hind limbs and the entire skeleton of the dwarf Pekingese dog disclosed that these skeletal structures are similar in each instance to those of the achondroplasic dwarf The adenohypophysis of the bulldog shows far reaching structural abnormalities whereas the bassethound s adenohypophysis adheres very closely to the normal canine pattern as represented by the German *shepherd dog None of these hypophyses were of a fixed pattern The histology* of the gland varied among the individuals of each dog breed but in spite of this individual variability *the hypophyses from contrasted breeds presented histologi* cal patterns which were quite consistently different in detail Stockard also noted that the physical form and type of the individual could be correlated with the histological pattern and cellular nature of the adenohypophysis In a two and one half year old female bulldog Stockard demonstrated widespread cystic forma tions in the pars distalis an abnormally small amount of secretory epithelium in the pars tuberalis and pars distalis and an excessive amount of connective tissue separating the cord like arrangement of epithelial cells of the pars distalis The acidophiles stained brightly and occurred in unusually high proportions in rela tion to the basophiles By crossing such an English bulldog with the bassethound Stockard separated and sharply localized each of their achondroplasic characters in the succeeding generations and *he demonstrated that* achondroplasic dwarfing could occur in certain parts and acromegalic overgrowth in other parts of the *skeleton of the same individual He concluded from these experiments that the* growth response of certain parts of the skeleton to an altered adenohypophysial secretion depended *primarily* on the genetic constitution of the tissues Some individuals among the F hybrids of this cross resembled either one or the other of the parent stocks in physical form as well as in histological pattern of the adenohypophysis There were also some odd individuals among these F_2 hybrids

mediated by a variety of adenohypophysial hormones, which differ in their quantitative effects, depending upon the type of animal to which, and the circumstances in which, they are administered He states[1 3] that the thyrotropic hormone and prolactin both play a part and act as mutual synergists in the growth of dwarfed mice whereas in pigeons prolactin alone is the growth promoting agent

Constitutional and Genetic Concepts

Stockard [3] departs from this conventional dispute by refuting completely the concept of an adenohypophysial, growth promoting hormone He states that growth is a universal property of protoplasm or life itself and occurs even where no specific adenohypophysial hormone is known to exist He admits, however, that in higher animals the kind and degree of growth can be regulated and modified by such a secretion Contrary to the generally accepted view Stockard believes that the adenohypophysis secretes a substance, which limits or inhibits rather than promotes growth and which regulates the amount of tissues and the size of organs by delicately balanced adjustments in the organism as a whole In so far as this so called growth hormone contributes to the normal balance of the internal chemical environment it secondarily influences the growth of tissues, which already have been committed genetically to a characteristic growth response Thus the transplantation of a Boston terrier hypophysis into a hypophysectomized dachshund could not possibly transform the dachshund into a Boston terrier According to Stockard both the distortions of growth and the adenohypophysial pathology to which they are attributed ordinarily arise primarily from a constitution determined genetically The experimental evidence marshalled in support of this hypothesis is impressive Stockard s conception of the functional and genetic relations of the adenohypophysis was not completely recorded because of his untimely death A review of his writings, however, gives a fairly precise notion of the thoughts he entertained on this subject He emphasized that the tendency to produce races and individuals of widely different types and size is especially characteristic of the human species and the dog Among human beings the most exaggerated deviations of type and constitution, e g giantism, dwarfism and acromegaly are associated with various pathological and functional changes in the endocrine glands From a clinical viewpoint it has been customary to attribute such marked changes in physical type to the diseased gland As a rule the emphasis has been placed on the functional deviations of the endocrines rather than on the hereditary element particularly in acromegaly In certain instances however there is every indication that hybridization or other genetic modifications play an important role in the pathogenesis of these maladies

There are some dog breeds which are free of skeletal deformities or symptoms

intimately correlated products of an hereditarial genetic background He believed that these three factors affect one another under the influence of an internal chemical environment the composition of which is regulated and controlled by the endocrine glands His observations indicate furthermore that the structural pattern and functional activities of the endocrine glands also are inherited characteristics and that a highly significant correlation exists between the inheritance of skeletal deformities and the occurrence of defective development of the adenohypophysis It may be inferred from Stockard s studies that any genetic change *or mutation, which affects the endocrines either directly or indirectly probably* is of the utmost importance in giving rise to a new species as well as to a new domestic breed His correlation of hybrid types and adenohypophysial histology clearly links body type and hypophysial pattern very closely

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who differed considerably from the parent stocks and developed growth deformities foreign to both breeds These unusual distortions of growth, commonly encountered in other breeds apparently arose from new combinations of qualities F hybrids of the achondroplasic bulldog bassethound stocks sometimes exhibited evidence of acromegaly in the form of excessive overgrowth and wrinkling of the skin heavy large bones of coarse structure, enlarged skull and malocclusion of the teeth F_2 hybrids also showed frequent abnormalities of their endocrine glands which included cryptorchid testes and cystic or arrested and otherwise modified development of the adenohypophysis In the adenohypophysis of one of these F hybrids which resembled an acromegalic St Bernard, Stockard found an almost perfect replica of the histological picture characteristic of human acromegalic giantism i e acidophilic adenoma or true hyperplasia of the acidophiles There were very few chromophobes in this species, and basophiles were hard to find Thus an acromegalic constitution was brought about through complex combinations of qualities in the bassethound bulldog F hybrids, which are derived from essentially normal sized achondroplasic parent stock This cross also produces examples of dwarfism Stockard points out that these opposite types of growth response are associated with similar histological derangements of the adenohypophysis He denies therefore that adenohypophysial hypersecretion induces giantism and acromegaly and that its hyposecretion results in dwarfism This deduction appears to be the only obvious flaw in his argument against the existence of a growth stimulating hormone inasmuch as he assumes that gross histological similarities of the adenohypophyses necessarily indicate an identity of functional behavior Actually there is no cytological or physiological evidence among his observations to substantiate this viewpoint

Other experiments bearing particularly on the nature of giantism were carried out by Stockard on great dane and St Bernard dogs These animals are much larger in size than any of their probable ancestors The great dane is a slender gracefully proportioned giant whereas the skin and skeleton of the St Bernard who is a giant of heavy proportions exhibit definite evidence of acromegaly The adenohypophysis of the St Bernard is cystic very often or shows other signs of modified or arrested development The F hybrid generation resulting from a cross between great dane and St Bernard, shows a variety of combinations of the characters derived from the two pure stocks Among the various types which appear in the F generation are slender great dane like giants, giants with marked stigmata of acromegaly and adipose eunuchoid creatures which resemble Frohlich s syndrome in man

Having studied these interrelations of genetic constitution and endocrine activity on both normal and highly modified dog breeds Stockard concluded that the skeletal structure, physiological function and behavior of an organism are

intimately correlated products of an hereditarial genetic background He believed that these three factors affect one another under the influence of an internal chemical environment the composition of which is regulated and controlled by the endocrine glands His observations indicate furthermore that the structural pattern and functional activities of the endocrine glands also are inherited characteristics and that a highly significant correlation exists between the inheritance of skeletal deformities and the occurrence of defective development of the adenohypophysis It may be inferred from Stockard s studies that any genetic change or mutation which affects the endocrines either directly or indirectly probably is of the utmost importance in giving rise to a new species as well as to a new domestic breed His correlation of hybrid types and adenohypophysial histology clearly links body type and hypophysial pattern very closely

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Part IV

CLINICAL DISORDERS OF GROWTH

Clinical Application of Physiological Principles

As one might anticipate from the delicately balanced highly integrated and complex activities of the adenohypophysis clinical evidence of disturbances in its normal functions are encountered not infrequently Prominent among these in interest if not in numbers are the disorders of growth Abnormalities of growth frequently are modified by conditions which are inherent in the functional pattern of adenohypophysial activity The clinical picture of the resultant syndrome thus is highly variable and depends to a considerable extent upon a number of factors of which the following are known well enough to record with some assurance

Disturbance of Growth regulation in Relation to Disorders of Carbohydrate, Water and Sex Metabolism

In addition to its growth regulating activities the adenohypophysial function frequently is upset coincidentally in other directions so that various combinations of disordered carbohydrate water and sex metabolism may become features of the clinical syndrome

Disturbance of Growth regulation in Relation to Functional Condition of Epiphyses

The physiological age of the individual as indicated by the state of epiphyseal diaphyseal union determines to a large extent the type of growth disturbance which can develop If the epiphyses are open and the growth regulating influence of the adenohypophysis is deranged in the direction of hyperfunction the clinical picture is that of giantism whereas if the epiphyses and diaphyses are united and the same hypophysial conditions prevail acromegaly is the end result When adenohypophysial hyperfunction begins before puberty and continues into adulthood the patient develops features of acromegaly in addition to giantism

Disturbance of Growth regulation in Hypogonadism

Primary hypogonadism, which is established before puberty, results in delayed union of the epiphyses and a clinical syndrome of eunuchism or eunuchoidism. By virtue of a secondary derangement of adenohypophysial function this combination of circumstances is favorable to the prolonged and consequently excessive stimulation of the growth cartilages of the long bones. The clinical picture of the resultant endocrinopathy is that of *eunuchoidal giantism*.

The abnormal persistence of unossified epiphyseal cartilages in castrated or eunuchoid individuals has been attributed universally to the absence or marked impairment of gonadal function. In support of this assumption it has been pointed out that precocious puberty is associated clinically with premature closure of the epiphyses and dwarfism, whereas normal sexual maturity likewise is related chronologically to epiphyseal union and cessation of growth. It is noteworthy, however, that the epiphyses of *infantilistic dwarfs* remain wide open far into middle age, even though their growth may remain stationary. The only physiological denominator common to infantilistic dwarfism and eunuchoidal or castrate giantism is gonadal insufficiency. The only anatomical denominator common to both conditions is the persistence of ununited epiphyses. The outstanding difference between these two endocrinopathies obviously is the excessive linear growth in castrated or eunuchoid individuals and the stunted growth in victims of infantilistic dwarfism. Generally it is stated that excessive growth occurs in the castrated or eunuchoid individual because the epiphyses remain ununited. That this is an unacceptable explanation may be gathered from the fact that ununited epiphyses likewise are characteristic of infantilistic dwarfism. One may assume safely from available evidence that the presence or absence of a growth stimulus in an individual with ununited epiphyses determines whether the end result is dwarfism or a form of giantism. In the present state of our knowledge one may conclude that the same pathological process which deprives the dwarf of his growth stimulus also robs him of his gonadotropic hormones. The result is infantilism and dwarfism. In the castrated or eunuchoid individual, however, the pathology primarily is in the gonads which, when removed or functionally incapacitated, stimulate an intact adenohypophysis to increased activity. In this functional hyperactivity lies the probable explanation for the excessive linear growth in eunuchoidal giantism. It is generally accepted that castration results in basophilia of the adenohypophysis as well as in an increase of its gonadotropic potency[1, 3, 4, 5, 6, 7, 8]. The functional pattern of the hypophysis appears to be such that hypersecretion of one of its hormones not infrequently is associated with or responsible for an increase in the rate of secretion of another of its hormones. Although the growth hormone has been linked in many ways with the

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acidophile it should be recalled that the disturbances in secretion of the thyrotropic and sex hormones are reflected cytologically by alterations in both the acidophiles and basophiles While there is no evidence to suggest that the basophiles, which are hyperactive in hypogonadism, may play a role also in the regulation of epiphyseal growth neither is there any direct evidence against this thought A disturbance in the function of the acidophiles coincident with or secondary to that of the basophiles would of course explain the excessive growth stimulus in a more orthodox fashion The fact that gonadectomy affects the adenohypophysial acidophiles as well as the basophiles is in accord with the latter suggestion

Relation of Sex Hormones to Regulation of Growth

There have been isolated from the adrenal cortex certain chemical principles which exhibit the biological activity of hormones secreted by the male and female gonads These corticosteroids include the androgenic substances adrenosterone and 17 hydroxyprogesterone[9 10] and the ovarian like hormones estrone and progesterone[11 1] which show estrogenic and progestational activities respectively A gonadotropin adrenoluterin also has been isolated from the adrenal cortex[13] It is important to note furthermore that these steroids of the gonads and adrenal cortex are related chemically by virtue of their common molecular configuration, the phenanthrene cyclopentane or cholane nucleus The fact that varying amounts of biologically active androgenic and estrogenic steroids continue to be excreted in the urine after gonadectomy lends credence to the belief that the adrenal cortex may be regarded as a definitive organ of sexuality

As noted above precocious puberty is associated with premature closure of the epiphyses whereas normal sexual maturity likewise is related choronologically to epiphyseal union Growth ceases in both cases These clinical data, coupled with the fact that the epiphyses remain wide open indefinitely in castrated or eunuchoid individuals who have little or no gonadal function have led to the widely accepted belief that sex hormones inhibit growth or at least are antagonistic to its progress There are other clinical observations however which not only fail to harmonize with this viewpoint but actually indicate that the sex hormones stimulate the rate of growth Rowlands and Nicholson[14] have reported an increased rate of growth in boys afflicted with testicular tumors, which produced excessive amounts of androgen Tumors of the adrenal cortex likewise are associated with enhancement of the rate of linear growth but early closure of the epiphyses is another feature of this condition Friedgood and Gargill[15] observed these phenomena in a 10 year old female, who developed extensive evidence of virilism 6 months after she began menstruating precociously at the age of 8 as a result of an adrenocortical tumor These clinical data indicate that androgenic

substances of testicular origin stimulate the rate of linear growth of the body They suggest also that the adrenocortical steroids which exhibit androgenic and estrogenic biological properties are associated in some way with enhancement of the rate of growth and premature closure of epiphyse That androgens stimulate the rate of linear growth has been proved beyond doubt by the effect of testo terone compounds in dwarfed children The administration of testosterone propionate or methyl testosterone in such circumstances results in an obvious acceleration in the rate of growth [61, 38, 9, 9] There is no evidence that these hormones induce premature closure of the epiphyses[1] nor has this undesirable effect been elicited by injections of chorionic gonadotropin which stimulates the development of the testes and accelerates the rate of linear growth coincidentally [21] It is well recog nized of course that the onset of puberty which is characterized by evidence of enhanced androgenic and estrogenic activity in both sexes generally is the period during which there is an exaggerated spurt in the rate of linear growth In the light of present knowledge this may be attributed in part to a state of increased gonadal activity Experience with the skeletal changes in cases of adrenocortical tumor of which the case cited above is an example[15] suggests that the adenocorti cal androgens and estrogens, either in combination or individually also are con cerned with the normal physiological mechanism which regulates and controls the growth and maturation of epiphyses in adolescence In any event it is of impor tance in this connection to note that the adrenal cortex has been credited with the *property of retarding the rate of epiphyseal chondrogenesis and osteogenesis in* hibitory effects which stunt the body growth [3]

The Problem of Prepubertal Gonadal Function in Relation to Growth

There is one aspect of the relation between gonadal function and growth which needs further elucidation It is assumed generally either overtly or tacitly that the gonads are lacking in function until puberty arrives and objective evi dence of their functional activity is to be seen in the blossoming of secondary sexual characteristics Such a viewpoint was expressed by Severinghaus in the statement Since the ovaries do not begin active follicular growth until about the twentieth day the young female rat may be regarded as a physiological cas trate It is possible however that the gonads may be functioning at a reduced level of activity prior to puberty The three so called springing up periods to which reference has been made already suggest that a growth promoting stimu lus goes into high gear on two occasions long before puberty is due Whether or not these are an expression of a temporarily heightened gonadal influence remains to be seen At any rate the subject is still too unexplored to merit a dogmatic attitude

ACROMEGALY

Definition

Acromegaly is a chronic disorder in which the adenohypophysis always is involved pathologically This syndrome ordinarily is attributed to a benign or malignant acidophilic adenoma only infrequently is it associated with simple hyperplasia of the acidophilic cells of the adenohypophysis Experimental genetic studies indicate that the adenohypophysial pathology as well as the constitution of the afflicted individual may be inherited characteristics The disease is characterized by hypertrophy of the skeleton, overdevelopment of the soft parts, splanchnomegaly and pathological as well as physiological changes in many of the glands of internal secretion other than the adenohypophysis, especially the thyroid adrenal cortex, parathyroids thymus and gonads

Historical Background

Acromegalics as well as giants have been objects of interest to the layman and artist since prehistoric times According to Sternberg [5,6] a portrait of an acromegalic painted in 1553 is the earliest known record of this disease The pathology of acromegaly was described clearly by Fritsche and Klebs several years before Marie [8] in 1886 recognized and named the clinical syndrome The following year Minkowski [9] ascribed the syndrome to hypophysial disease In his original communication Marie reported 2 cases of his own and collected 5 others which had appeared previously in the literature under various names, and in subsequent publications[30,31,3] which increased the number of his reported cases to 17 he also directed attention to the enlarged hypophysis as a pathogenetic factor in the disease Marie s contributions stimulated the appearance of increasing numbers of reported cases

By 1893 Collins had 83 cases available for review, and in 1897 Sternberg [5,6] collected 200 cases of which 47 had been autopsied In 1932 Atkinson [4] analyzed the data on 1 319 cases with 265 autopsies Benda[35,36] was the first to direct attention to the predominance of acidophilic cells in the adenohypophysial adenomas in 3 of the 4 cases he reported In spite of Benda s report and Fischer s[37] subsequent emphasis of this point there was considerable controversy over the pathogenesis of this disease until those earlier pathological studies were reviewed and extended by the investigations of Cushing Bailey Davidoff and Putnam[38,39,40], who were in better position to interpret the physiological and clinical significance of their observations

Incidence and Predisposing Factors

Acromegaly is a rare disease. Atkinson[4] uncovered only 1 606 instances of this disease after a careful search of the literature up to 1938 in addition to the aid of the British Consular Service all over the world. Autopsies had been performed on less than 25 per cent of these cases. At the University of California Hospital over a 5 year period from 1937 to 1941 12 cases were so diagnosed among 35 757 entries or an incidence of 1 in 3 000. The diagnosis was made only 14 times among 210 094 admissions to the Boston City Hospital over a 6 year period from 1930 through 1935.

Males and females are about equally affected and it may occur in the black and yellow races as well as the white. Cases have been reported in late childhood, but they are certainly exceedingly rare before the second decade. The onset occurs in the third decade in about 50 per cent of the patients.

The only predisposing factor known is that of familial tendency. A history of acromegaly or of various types of hypophysial disease in other members of the family is obtained sometimes[3,3,36,41,4,3,45]. Benda[5,6] reported 4 cases in one family.

The onset of the disease may be preceded by, or coincide with, trauma to the skull, pregnancy or an acute infectious disease, but there does not appear to be any detectable precipitating factor in the majority of cases.

Correlation of the Pathology and Pathological Physiology. Their Clinical Significance

The Adenohypophysis. — The hypophysis rarely is of normal size in acromegaly. Ordinarily it is enlarged because of a benign adenoma or malignant neoplasm. These tumors, which usually are solid, not infrequently are softened by cystic or hemorrhagic areas. Generally the tumors are relatively small, in which case they may extend above the diaphragma sellae or less frequently into the sphenoid cells. Rarely they become enormous, erode the sella turcica and invade the cranial cavity. The common cytological *denominator of the normal sized* as well as the tumorous hypophysis is hyperplasia of the acidophilic cells[33,46,47,48]. According to Putnam and Davidoff, the tumors are of three different types. Type I consists of a highly cellular, loose mass of large cells, practically all of which are packed with acidophile granules. Most of the cells have hyaline centers, many are multinucleated. The tumors of type II, although practically free of stroma like those of type I, differ from the latter in that the mass is more compact and many non granular cells occur among those which are acidophilic. In tumors of type III there is only a thin rim of cells containing acidophile granules.

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Date	B.M.R	Pulse Rate	Therapy	Experimental period in days	Comment
5/2/30	+43	95	None		Control
7/30/30	+39	92	None		Control
7/30/30	—	—	Lugol's solution 10 drops twice daily	0	Lugol's solution started immediately after last B.M.R. determination
8/5/30	+38	92	Increase Lugol's solution to 15 drops, twice daily	6	
8/6/30	+32	80		7	
8/7/30	+25	76		8	
8/9/30	+24	80		10	
8/12/30	+27	80		13	

Iodin induced a progressive decrease in basal metabolic rate to a level of +18 per cent in 9 days after which the rate of oxygen consumption returned to a level of approximately +30 per cent in spite of continued iodin therapy. Davis[5, 54] has reported 3 cases of acromegaly treated in similar fashion and observed only a moderate decrease in the rate of oxygen consumption in one of them. The significance of adenohypophysial hyperactivity in relation to the hyperthyroidism of acromegaly is demonstrated further by the observations of Cushing and Davidoff[5, 6], who found that operations on the chromophilic hypophysial adenoma itself was followed by a decrease in basal metabolic rate which was almost as uniform as the effect on metabolism of thyroidectomy in exophthalmic goiter. Their data indicate however that the elevated oxygen consumption in acromegaly usually is not reduced to normal by thyroidectomy. This is in accord with what is known of the extrathyroidal metabolic effects of the adenohypophysis[57, 58, 59].

In attempting to evaluate the incidence of goiter and hypermetabolism in acromegaly it is essential to recall that the onset of this disease is insidious that the course is one of prolonged duration and that it is marked by unpredictable waves of remissions or exacerbations. Since studies of individuals with this disease ordinarily are made at times when pressure symptoms in or about the sella turcica, physical disfigurement or cardiac complications call the patient's attention to his ill health it is possible that episodic disturbances in thyroid physiology may be overlooked. Furthermore, many patients are relatively well advanced in their course before they come under observation and it is well known that the hyperthyroidism in such circumstances is quite likely to have disappeared or to have been replaced by hypothyroidism. The foregoing considerations may well

around a central mass of small agranular cells The clinical activity of the disease is said to be proportional to the number of acidophilic cells found in the adenohypophysis[40]

Pathological changes are to be found in endocrine organs other than the adenohypophysis These alterations appear for the most part to be secondary to the hypophysial pathology

The Thyroid — In 1897 Magnus Levy ' pointed out that certain physical signs and symptoms characteristic of exophthalmic goiter also are to be found associated inconstantly with acromegaly Enlargement of the thyroid gland, elevation of the basal metabolic rate and tachycardia not infrequently complicate the clinical picture of acromegaly during the active phases of this disease, exophthalmos is an unusual but occasional physical finding The basal metabolic rate varies tremendously so that reports of arithmetic means on large groups of patients are misleading and have no significance other than to indicate that there is a definite trend towards hyperthyroidism in the early phases of acromegaly and towards hypothyroidism in the late stages The range covered is from −30 per cent to +80 per cent and the rate in any one individual apparently depends on the duration of the disease and the state of adenohypophysial function As the activity of the chromophilic adenoma burns itself out and the remainder of the hypophysial parenchyma is destroyed by pressure atrophy, the acromegalic develops a secondary hypothyroidism Discovery of the thyroid stimulating effect of adenohypophysial extracts and the fact that thyroid atrophy results from hypophysectomy have established a rational explanation for the occurrence of hyperthyroidism in acromegaly Probably it is due to stimulation of the thyroid gland by an excessive secretion of the adenohypophysial thyrotropic principle, and the ophthalmotropic activity of the adenohypophysis[12] could account satisfactorily for the exophthalmos which is encountered occasionally This parallelism between the hyperthyroidism of acromegaly and that of exophthalmic goiter is enhanced further by the observation that iodin induces an identical decrease in the elevated basal metabolic rate of both diseases In 1927 Cushing and Davidoff reported a case of acromegaly in which iodin decreased the elevated basal metabolic rate just as it does in exophthalmic goiter and in 1930 Friedgood [2] encountered a second early instance of acromegaly before erosion of the dorsum sellae was detected which responded in a similar fashion The diagnosis was confirmed subsequently at autopsy An abbreviated tabular protocol of this case follows

A third case of acromegaly with hyperthyroidism which responded favorably to iodin therapy came to this writer s attention through the courtesy of Dr James H Means The initial basal metabolic rates ranged from +30 to +45 per cent with an average of +39 per cent on four successive determinations

dial failure than the hyperthyroidism It is probable however that hyperthyroidism also is an important contributing factor Adequate treatment of the myocardial insufficiency depends therefore on the control of the hyperthyroid state as well as of the hyperactive adenohypophysial condition

The Parathyroids —Enlargement of the parathyroids in acromegaly was described originally by Erdheim[69] and adenomas of this gland have been reported occasionally according to Cushing and Davidoff [6] Hadfield and Rogers [0] on the other hand, have questioned the pathological diagnosis of adenoma That this parathyroid pathology may be related to perverted adenohypophysial function is suggested by observations on experimental adenohypophysial hyperactivity Adenomas of the parathyroids have been found in experimental acromegalic animals [7], and adenohypophysial extracts similar to those which have produced the latter also induce hyperplasia of the parathyroid in rabbits [1] Friedgood and MacLean [2] [4] have demonstrated an elevated blood calcium level in guinea pigs subjected to treatment with alkaline extracts of the adenohypophysis The blood phosphorus level was not altered coincidentally

The Adrenals —The adrenals particularly the cortex ordinarily are enlarged markedly in acromegaly Microscopic and macroscopic cortical adenomas are frequent findings Here as in the case of the thyroid and probably of the parathyroids it is likely that an overabundant adenohypophysial secretion is at fault In 1929 Putnam Benedict and Teel observed adrenocortical adenomas in dogs which were injected over a period of months with an alkaline extract of adenohypophysis In 1932 Evans and associates [8] noted that the injection of growth promoting extracts resulted in cellular hypertrophy of the fasciculate zone of the adrenal cortex with some increase in the amount of cortical lipoids In 1933 Emery and Atwell[77] Friedgood[74] [8] and Houssay and associates [9] reported independently that the daily injection of only partially purified adenohypophysial extracts caused a marked hypertrophy and hyperplasia of the adrenal cortex which was significant statistically[74] This was confirmed abundantly by numerous subsequent investigators with more highly purified adenohypophysial extracts containing the adrenocorticotropic hormone A detailed account of the latter is included in a discussion of the adrenocorticotropic hormone in Part II

The Gonads —The ovaries and testes have been regarded generally as atrophic although there are no adequate clinical or autopsy records to substantiate this viewpoint As a matter of fact hypergenitalism in the male acromegalic with hypertrophy of the testes is not an infrequent clinical observation In one of the cases reported by Cushing and Davidoff [6] there was an hypertrophy and in another an atrophy of the spermatogenic epithelium and interstitial tissue Teel has observed hypertrophic changes in the female generative tract Schultze and Fischer state that in a man of 56 in whom the acromegaly was of seven years

account for whatever discrepancies there are in the literature on the incidence of clinical hyperthyroidism in acromegaly Davidoff found thyroid enlargement present in 25 per cent of 100 cases Davis in 50 per cent of 166 cases[4, 55] and Cushing and Davidoff [6] reported an elevated basal metabolic rate in 70 per cent of 72 patients Boothby and Sandiford[61] observed hyperthyroidism in 50 per cent of 30 cases

Enlargement of the thyroid may be diffuse early in the disease, but simple hypertrophy and hyperplasia are encountered uncommonly, probably because thyroidectomy usually is not done until relatively late in the disease The histological appearance of the enlarged thyroids varies considerably The most common finding is that of fairly well circumscribed nodules of parenchymatous hypertrophy and hyperplasia scattered throughout the substance of a colloid gland or a gland which is itself the seat of widespread hypertrophic and hyperplastic parenchymatous changes Colloid degeneration is met with frequently and is the end result of a succession of many periodic waves of activity alternating with involution This cyclic variation in thyroid function apparently is a reflection of the successive remissions and exacerbations characteristic of the course of acromegaly In accordance with the observations of Marine and Lenhart[6, 63, 64] and Reinhoff[?, 66, 67] these alternating phases of thyroid activity, hypertrophy and hyperplasia followed by the colloid state etc probably result in the so called adenomatous goiter Certainly such nodular areas do not represent true tumors such as the adenomas They are localized regions of hypertrophy and hyperplasia set off from the surrounding parenchyma by connective tissue This type of goiter is the most frequent form of thyroid enlargement in acromegaly Those instances in which the thyroid gland is of normal size can be explained satisfactorily by a fundamental rule of hypophysial physiology viz when one of the several functions of the hypophysis is disordered the gland may or may not exhibit a concomitant disturbance in the secretion of one or more of its other physiologically active substances The pattern of dysfunction i e the number and type of physiological disturbances is unpredictable in any one case and varies from patient to patient It is also possible that pressure atrophy may interfere with the excessive elaboration of the thyrotropic hormone early in the course of the disease thus obviating the abnormal stimulation of the thyroid gland

Since myocardial insufficiency not infrequently is a complication of persistent hyperthyroidism it might be anticipated that its incidence would be relatively high in acromegaly Courville and Mason[68] have found that among 24 cases of this disease 6 died of cardiac failure and 18 showed some evidence of it during their period of observation They concluded however that the increased work imposed on the heart by the generalized splanchnomegaly and overgrowth of the heart itself were quite likely the more immediate factors responsible for myocar

largement of the external occipital protuberance increases the circumference of the skull significantly and alters the physiognomy of the patient to a remarkable degree The disproportionate enlargement of the mandible results in marked malocclusion The teeth become widely separated not so much due to the enlargement of the jaws as to a heaping up of the alveolar arches[5]

The bones of the extremities generally are enlarged in diameter because of overexpansion of the cancellous bone in addition to an increase in periosteal bone growth The latter appears to be due to an abnormal exaggeration of the normal transverse growth of bone whereas in gigantism there is an increased cartilaginous bone growth which results from an abnormal exaggeration of normal longitudinal bone growth An increase in the length of the long bones also occurs in acromegaly if the disease gets started before closure of the epiphyses Other evidence of abnormal proliferation of bone tissue occurs in the form of numerous wart like projections exostoses at the site of muscular and ligamentous attachments and around joints The surface of the bones is markedly irregular and rough at the ends of bones and wherever spongy tissue is abundant as in the vertebrae the basilar portion of the occiput and the bones of the feet Thickening of the bones is particularly apt to occur at the site of the fused epiphyses This terminal thickening results in that tufting of the phalanges of the hands and feet which is roentgenologically pathognomonic of the disease Erdheim[84] has described a form of arthritis in acromegaly which is caused by periosteal ossification with pathological proliferation of the cartilage

The vascular channels of the bones are visible and large The medullary canals of the diaphyses are dilated and so are the Haversian canals which appear on the surface in distinctly punctate form Fritsche and Klebs[7] have called special attention to the markedly dilated blood vessels in acromegaly

Roentgen Studies of Skeletal Abnormalities —Oppenheim[7] was the first to recognize enlargement of the sella turcica during life by means of roentgenography Since that time it has proved invaluable in the differential diagnosis of hypophysial disease[88,89,90,91,92,93,94] The x ray changes of the bone in and about the sella depend for the most part on the direction in which the expanding tumor exerts its pressure Thus a purely sellar tumor may widen the sella and deepen the floor so that the bony partition between the sella and the sphenoidal sinuses is reduced to extreme thinness or to actual perforation The clinoid processes remain intact in such cases although the tumor is large Tumors which grow upward widen the entrance to the sella erode the clinoid processes and finally destroy them In a third variety there is more or less complete absorption of the dorsum sellae and a downward displacement of the base of the sella so that there is obliteration of the sellar landmarks with the usual exception of the anterior clinoid processes In some instances there is a downward displacement of the entire sphenoidal re

duration, there was strikingly abundant spermatogenesis and an enlarged prostate, which was in a condition of abundant secretion. Atrophy of the internal genitalia has been reported in 36.4 per cent of the 118 female acromegalic patients according to Creutzfeld[81]. Tandler and Grosz[8] found total regression of the primordial follicles and cessation of formation of the Graafian follicles. They noted also degeneration of the interstitial cells of the testes and of the epithelium of the seminal vesicles. Hypergonadism apparently is more common in the male than in the female, in whom there is a high incidence of amenorrhoea and other menstrual disorders. It is not surprising that both hypertrophy and atrophy of the gonads occur in association with acromegaly; they should not be regarded as mutually contradictory findings. It is conceivable that in one phase of the disease the acidophilic hypophysial adenoma may be in a state of hypersecretion or cause an irritative hypersecretion of the surrounding glandular parenchyma, whereas later there is hyposecretion due to internal disintegration of the adenoma or pressure atrophy of the surrounding parenchyma, as the case may be.

The Liver, Spleen, Kidneys, Thymus and Pancreas. — The thymus frequently is persistent and may be relatively much enlarged. Generalized lymphoid hyperplasia often is an associated feature. The spleen and kidneys may or may not be hypertrophied, but the liver usually is increased in size and in one instance[84] was found to weigh 6,200 grams in comparison with a normal weight of about 1,500 grams. Cushing states[83] that with the exception of an unusual infiltration of fat no definite change was observed in the pancreas of 8 hyperpituitary individuals. He adds that possibly in all of them the islets were more in evidence than in the average supposedly normal gland. Goldberg and Lisser[84] report that in one diabetic acromegalic patient autopsy disclosed a few small islets in a gland which otherwise looked grossly normal.

The Skeleton. — The skeletal pathology of acromegaly has been studied most extensively by Sternberg.[5, 26] The skeletal hypertrophy, which is generally symmetrical, is particularly well marked in the skull and extremities. In advanced cases the entire skeletal system may be enlarged, particularly in the transverse diameters, and most of the cartilage of the body is ossified.[40] The experimental form of acromegaly, which has been produced in animals by long continued injections of chemically crude extracts of the adenohypophysis, is characterized by remarkably similar skeletal alterations. These have been described in detail in a previous section of this chapter.

The skull is affected in several ways. The flat bones of the calvarium are increased in thickness and overexpansion of the cancellous bone is particularly notable in the prognathous mandible. Hyperpneumatization of the skull occurs through enormous enlargement of the nasal sinuses and mastoid cells. The gradual but progressive development of these changes, in addition to a marked en

muscular stresses and strains induce scoliosis of the spinal column and deformity of the mandible other than its general enlargement

Skin Mucous Membranes and Connective Tissue — In addition to the general skeletal enlargement there is also a considerable thickening of the inter osseous connective tissue and of the overlying soft parts The skin may be raised readily from the underlying tissues in thick folds These external thickenings are

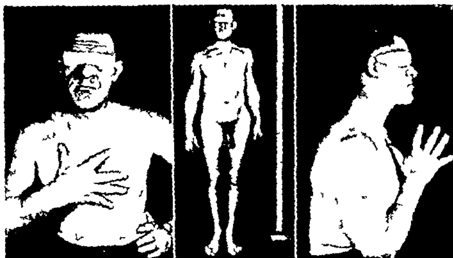


Fig 6 Acromegaly Note the hyperpigmented skin hypertrichosis coarse features of the physiognomy paw like hand the shape of the skull and mandible and the development of the genitalia Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

largely responsible for the coarse features of the acromegalic and contribute to the configuration of the paw like hands and sausage shaped fingers (Fig 26) There is also an augmentation in the connective tissue of the subcutis which ex tends to and may involve the muscles The tissues thus feel dense and boggy to palpation and the natural lines and creases of the face and hands are increased to the depth of furrows particularly over the forehead

The size of the hair follicles is increased the papillae are hypertrophied and the sebaceous glands are enlarged and hyperactive The skin pigmentation be comes progressively deeper in the active stages of acromegaly in contrast to the ghostly pallor unrelated to anemia and probably due to depigmentation which is characteristic of adenohypophysial insufficiency Late in the disease, when glandular insufficiency supervenes, the acromegalic also acquires this abnormal skin pallor which may be accentuated by a secondary anemia

gion In the early stages of acromegaly particularly in the absence of a significantly enlarged hypophysial mass there may be thickening of the walls of the sella, probably as an expression of the general tendency toward osseous overgrowth In one instance case xxx cited by Cushing[84], there had been such a degree of bony overgrowth that the actual enlargement of the sella was masked until it was disclosed by stereoscopic plates Roentgenography is particularly helpful in the diagnosis if the tumor is calcified

Normal configuration of the sella turcica by x ray is not incompatible with the diagnosis of acromegaly, since this syndrome may be initiated without tumor formation by microscopic alterations in the adenohypophysis Furthermore an extrasellar acidophilic tumor arising in the sphenoidal sinuses from vestigial remnants of the so-called craniopharyngeal duct is believed to result in acromegaly Erdheim[69 86 89] reports such an instance in which the tumor eroded the floor of the sella from below and established contact with the hypophysis in this unorthodox fashion

The general configuration of the skull and the size of the sinuses yield important radiological information concerning one aspect of the adenohypophysial dysfunction in acromegaly[95 98] The skull shows widespread hyperpneumatization The frontal sinuses bulge and the mastoid cells and sinuses of the facial cranium are overdeveloped also These changes in addition to the overexpansion of cancellous bone in the lower jaw alter the radiological configuration of the face strikingly A diffuse generalized skeletal sclerosis which includes the skull, complicates these primary changes so that there is massive thickening of the cranium and other parts of the skeleton Although it has a special predilection for the mandible the overexpansion of cancellous bone is also of generalized distribution where it is characterized by marked bone proliferation in the region of the fused epiphyses and terminal phalanges Consequently there is marked thickening of the bones especially near the fused epiphyseal lines The overexpansion of cancellous bones in the hands and feet which takes place during the early stages of the disease subsequently is obliterated by the superimposed sclerosis and results in tufting of the phalanges which is a pathognomonic x ray sign

Osteophytes indistinguishable from those encountered in hypertrophic arthritis may extend into tendons and ligaments Occasionally they are extensive enough to fuse several vertebrae together These observations suggest that the adenohypophysis may be responsible for the hypertrophic arthritis of middle age inasmuch as the function of this gland is disturbed to a significant degree by the advent of the menopausal or climacteric period Other important changes occur in the spine which Atkinson[14] found affected in 80 per cent of the cases The vertebrae become enlarged in all diameters The most frequent deformity of the spine is an upper dorsal kyphosis with a compensatory lumbar lordosis Abnormal

Hair —The growth of hair on the head often is remarkably thick and the individual hair strands are coarse In males there is an increase in the hair of the trunk, abdomen and extremities where hair is already present or an abnormally heavy growth appears in these regions during the course of the malady The pubic and axillary hair growth characteristically becomes more dense In females there may be hair growth of a virilistic type and distribution in association with an appreciable increase in the size of the labia majora and clitoris

Muscles —In most cases the muscle strength is not diminished in the initial stages acromegalic individuals sometimes may even exhibit extraordinary strength in the early stages of the disease Early in the syndrome, however there may be a gradually increasing fatiguability and eventually muscular weakness is a predominant debilitating symptom The muscles of the arms and legs become markedly atrophic in the terminal stages a change which renders more conspicuous and serves to accentuate the bizarre skeletal deformities of this disease (Fig 27) Microscopically such muscles show an increase in their connective tissue and fat content with degeneration and atrophy of the individual fibers [8]

Clinical Course

So diversified are the clinical manifestations of acromegaly that the pattern of the developing syndrome exhibits innumerable variations The complex symptomatology can be accounted for on a rational physiological basis only by taking into consideration the following factors

(1) An expanding adenohypophysial tumor produces so called neighborhood signs and symptoms by virtue of the strategic anatomical position of the gland with reference to the surrounding osseous and intracranial structures

( ) The fact that the adenohypophysis is concerned with many metabolic functions and reciprocal neuroendocrine relations accounts in large part for the complex mosaic pattern of endocrine and hypothalamic disorders which are characteristic of acromegaly

(3) The changing secretory function of the sellar tumor which eventually ceases to be active and the increasing pressure atrophy of the undiseased portions of the adenohypophysis determine the general course of the malady This is characterized by a progressive but fluctuating intensity with alternating periods of exacerbation and remission which end in a terminal phase of adenohypophysial insufficiency

(4) The clinical coexistence of hyperactive and hypoactive adenohypophysial functional levels may be confusing but it is to be expected from what is known of the cytology and physiology of this gland

The unfolding clinical picture of this syndrome thus takes various forms which

Hochenegg[9, 98, 9], O Hirsch[100, 101, 10, 103, 104] and Cushing[83] have noted a certain retrogression in the cutaneous manifestations of this disease either during the spontaneous transition to the state of glandular insufficiency or in the immediate period following removal of the tumor The latter led Cushing to believe that a large part of the thickening and bogginess of the subcutaneous tissues must be due to an associated edema

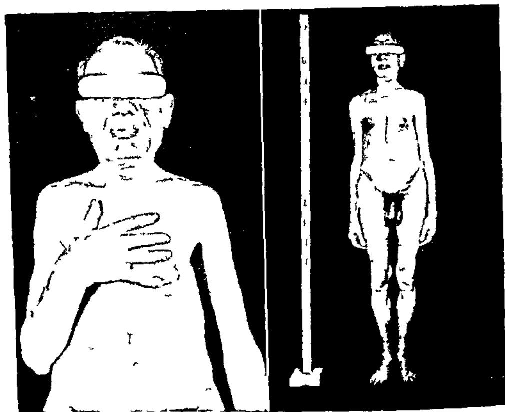


Fig 27 Acromegaly in an advanced state as a result of acidophilic adenoma Note wasting of musculature and subcutaneous tissue Compare with Fig 26 Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

The mucous membrane of the oral cavity is universally thickened The papillae of the tongue became hypertrophied Because of the marked hypertrophy of its muscular substance the tongue may protrude between the teeth in spite of the enlarged jaws Vocal articulation may be affected because of this increase in the weight and size of the tongue Often the larynx also is considerably enlarged, and the voice is deep, unless secondary gonadal atrophy supervenes

heat in the fingers and matutinal joint stiffness Severe arthritic or bone pain and profuse sweating both of which are more apt to be troublesome at night contribute to an enervating insomnia In women night sweats due to ovarian failure may complicate the clinical picture Ordinarily excessive perspiration occurs in acromegaly during periods of exacerbation of the pathological process and diminish or disappear during phases of quiescence

The headaches are in general of three distinct types of which there may be various combinations viz those due to an expanding sellar neoplasm or hyperplasia glandularis those induced by generalized increased intracranial pressure and those brought about by a mass of tenacious white mucus which is retained under pressure in the sphenoidal sinuses

The headaches due to the first of these causes usually occur early in the course of the disease inasmuch as the expanding lesion is confined initially to the rigid walled sella turcica By way of contrast it should be pointed out that benign interpeduncular and intradural tumors which affect the hypophysis only secondarily do not induce intracranial discomfort of any consequence until relatively late in the malady It is noteworthy however that the fossa may be greatly enlarged by the persistent pressure of a slowly growing tumor without significant discomfort even at the outset Ordinarily the headaches of hypophysial origin are severe persistent and bitemporal Sometimes they may subside spontaneously presumably because the pathological process in the gland has ceased to expand while the sella turcica and the dural capsule of the hypophysis have become distended adequately enough to accommodate their contents without undue tension or these headaches may disappear spontaneously because the tumor decompresses itself by herniating through the glandular capsule into an enlarged eroded sella Cushing s operative experience indicates that this type of headache is due for the most part to a stretching of the capsule of the gland inasmuch as splitting this tensely distended envelope results in immediate relief from pain

The second type of *headache is less well localized since it is related to a* generalized increase in intracranial pressure transmitted through partial obstruction of the ventricle It usually comes late in the disease and is associated with a papilledema which is superimposed on the primary optic atrophy characteristic of the earlier stages of the acromegalic syndrome

The third type of headache is frontal in position It is due to an increased intrasphenoidal pressure brought about by a mass of tenacious white mucus which is retained within the sphenoid cells because of partial occlusion of the sphenoidal foramina by a downward displacement of the sellar base It is not unusual for these headaches to be relieved spontaneously and intermittently by the periodic nasopharyngeal discharge of mucoid masses often blood tinged

The *visual disturbances in acromegaly may be precipitated in a more or less*

are determined in large measure by the extent to which and the order in which the foregoing factors are involved There is a basic pattern, however, which may be regarded as fairly typical

The onset of the disease usually is insidious, and its chronic course commonly is of long duration In the early stages of the disease either the victim or others of his acquaintance note a beginning change in the features The skin becomes coarse and thick the facial expression heavy and the forehead deeply furrowed The lips gradually thicken the ears and nose enlarge, and the dimensions of the hands and feet increase judging by the fit of rings gloves and shoes Occasionally before its true nature is revealed, the increased size of the hands and feet is thought to be due to edema The supraorbital ridges, the occipital protuberance and the malar bones protrude markedly The mandible is thrust forward in a characteristic fashion with consequent malocclusion Abnormal growth of the tongue may result in an embarrassing impediment to speech The skin pigmentation increases

At recurrent intervals in the syndrome the adenohypophysial dysfunction induces bouts of hyperthyroidism with nervousness, palpitation, tachycardia, tremor occasional exophthalmos and finally, myocardial embarrassment Later, however as the adenohypophysial lesion regresses in function, a state of myxedema supervenes in which the patient suffers from the cold, dryness of skin, absence of perspiration and an anemia which is recalcitrant to treatment Much the same sequence of events occurs in the realm of gonadal function Hypergenitalism characterized by an increase in the size of the external genitalia and heightened libidinous tendencies may occur at the onset but more often this phase is relatively transitory particularly in women It is succeeded by amenorrhea in the female impotence in the male, a progressive regression in the size of the external genitalia and anaphrodisia in both sexes

Although most of the foregoing acromegaloid changes are permanent there are circumstances in which a partial regression has been noted Alterations in the facial appearance and slight enlargement of the hands and feet are not infrequent in pregnant women and more or less complete recovery usually occurs in the post partum period Remarkable reversible acromegaloid changes have been noted post operatively by Cushing[87] Bailey and Cushing[39] have reported a fugitive type of acromegaly of short lived activity which is produced by mixed adenomas composed of acidophile and chromophobe cells They have assumed that degranulation of the chromophiles leads to their loss of overactive function, which is followed by a state of insufficiency and clinical regression

Acromegaly may manifest itself first through severe persistent or periodic headaches visual disorders and parasthesias of the face and extremities particularly of the hands The acroparasthesias often are associated with sensations of

defects are of important differential diagnostic significance The primary defect usually involves the color fields first the form fields are affected later Although there are variations and exceptions to the rules, the involvement ordinarily begins in the color boundaries of one upper temporal quadrant This is followed by more or less complete temporal hemichromatopsia and a beginning defect in the upper temporal form field The process gradually spreads downward until most of the temporal field is involved Post-operative restoration usually occurs in the reverse order

The history of bouts of excessive epistaxis appears repeatedly in accounts of the early phases of this malady whereas a later manifestation is anosmia due to local involvement of the cerebral nerves secondary to extrasellar extension of the adenohypophysial tumor Consequently anosmia is associated commonly with primary optic atrophy

Uncinate gyrus seizures characterized by gustatory and olfactory aurae with or without subsequent seizures are surprisingly common among Cushing s cases[83] In all such instances there was an interpeduncular extension of the hypophysial growth which doubtless pressed upon and consequently irritated the adjoining uncinate gyrus In a number of his patients the seizures were characterized by subjective gustatory and olfactory impressions associated with a dreamy unreal sensation but without subsequent epileptiform convulsions Cushing believes that the epileptiform tendencies without recognizable uncinate factors which he has noted in certain instances of primary hypophysial hypoplasia are due to the existent hypophysial insufficiency because there were no tumors to involve the uncinate gyrus secondarily

Direct or indirect involvement of the hypothalamus with its attendant symptoms of somnolence periodic or persistent polyuria and polyphagia generally comes relatively late in the course of events Although polyuria may develop early in the disease because of pressure atrophy of the posterior lobe it is said to disappear again with destruction of the adenohypophysis Polyuria and polyphagia may be associated also with the decreased sugar tolerance which usually appears somewhat early but may come late in the course of events This complication is characterized by hyperglycemia with or without significant glycosuria Eventually it gives way to an increased sugar tolerance during the late stages of adenohypophysial insufficiency In view of the recent importance attached to the hypothalamic origin of polyphagia it would be of interest to question whether or not the hypothalamus is concerned with the polyphagia of diabetes mellitus in cases other than acromegaly

Moderate adiposity is a consistent feature of active acromegaly upon which may be placed one of several interpretations The voracious hunger of some individuals afflicted with this disease has been attributed for the most part to

abrupt fashion with the appearance of homonymous hemianopsia or a slow but progressive loss of vision may herald the clinical onset of the disease Photophobia which is one of the occasional troublesome symptoms, is associated often with deep orbital discomfort and sensitiveness of the eyeballs to pressure Transient, recurrent episodes of diplopia also are encountered occasionally in the early stages of the disease On the other hand these visual disorders may not occur until relatively late in the course of the malady In any event they are obviously *among the most important of the serious complications of this disease* The most common of the visual disorders and obviously the most grave, are those manifesting interruption of the fibers of the optic nerve It has been determined by *Cushing*[83] *that the degree of involvement of these nerves bears no direct* relation to the size of the sella turcica The optic fibers apparently are more apt to suffer from an extrasellar mass than from a primary, adenohypophysial, acidophilic tumor Thus in many acromegalics one may encounter an enlarged sella without visual disturbances Chromophobe hypophysial adenomata, however, not infrequently cause profound involvement of the optic structures, possibly because they enlarge in the upward direction more rapidly than acidophilic tumors

Primary optic atrophy with some distortion of the visual fields usually is demonstrable in patients showing pronounced neighborhood symptoms Papilledema ordinarily is superimposed on the primary atrophy in the late stages, when the tumor has become large enough to induce increased intracranial pressure According to Cushing[84] the latter is due in the majority of instances to occlusion of the foramen of Monro with resultant hydrops of the lateral ventricles This complication usually provokes an abrupt onset of generalized pressure symptoms with an increase in headache and possibly vomiting The immediate cause of the papilledema is distension of the sheath of Schwalbe by persistent pressure through the cerebrospinal fluid That this is the mechanism may be gathered from case viii of Cushing's series *in which neuroretinal edema did not occur* during a phase of increased intracranial pressure because the optic nerve was completely enveloped in the tumor mass It appears also to some extent at least, that the amblyopia associated with primary atrophy represents a physiological *block to light impulses rather than an actual destruction of the nerves* Partial vision, including restoration of the visual fields not infrequently is restored promptly by operation even though there has been a brief preoperative period of total amaurosis

Bitemporal hemianopsia with a macular vertical meridian is not as common as many believe It is due to a bilateral upward extension of the tumor mass to the optic chiasm Homonymous defects are almost as frequent as bitemporal ones, and unilateral amblyopia may occur with little if any perimetric deviation in the opposite eye Cushing has emphasized that even tendencies toward temporal

in a patient whose symptoms are somewhat obscure presents the clinician with a diagnostic problem of some moment The differential diagnosis must be made preoperatively in order to determine upon the proper course of therapy For instance the acidophilic adenomata are quite sensitive to roentgen therapy whereas the chromophobe tumors are much less so[1, 1] Aneurysm of the chiasmal area at times closely resembles hypophysial adenoma because it may produce great enlargement of the sella optic atrophy and visual field defects Aneurysm may be differentiated from other chiasmal tumors by x ray examination which may show a characteristic crescentic shadow from calcification in its wall or by arteriograms taken *during the injection of thorotrast into the common carotid artery* Naturally they call for a special form of therapy

The group of tumors consisting of chiasmal gliomas suprasellar meningiomas and cholesteatomas or chordomas should be recognized preoperatively so that there may be intelligent preparation for the special problems involved in their excision Any of these tumors by virtue of their anatomical location may be confused with acidophilic adenomata because they produce the same neighborhood signs and symptoms as a result of pressure upon the optic nerves and hypothalamus *With the exception of the* craniopharyngiomas which interfere with rather than accelerate growth and the chromophobe adenomata which affect adenohypophysial function by pressure atrophy the other masses usually do not induce hypophysial dysfunction Furthermore the craniopharyngiomas generally are cystic and give x ray evidence of calcification above the sella and the latter while *deformed is not often symmetrically distended as in the case of the hypophysial* adenomas Moreover these cysts tend to grow posterior to the chiasm in the direction of the third ventricle where their pressure produces an internal hydrocephalus with generalized increased intracranial pressure and choked discs instead of primary optic atrophy

The meningiomas in contrast to the craniopharyngiomas are found almost exclusively in adults although either tumor may occur in both age groups The meningiomas generally produce optic atrophy and bitemporal hemianopsia but *the sella is likely to be normal in size or only slightly deformed* *The wide sellar* expansion characteristic of adenomas ordinarily is not seen in connection with gliomas of the optic chiasm and nerves cholesteatomas and chordomas Although optic atrophy usually is present the visual field defects take unexpected forms and evidence of endocrine dysfunction rarely is well marked and usually limited to the hypothalamus

In the late phases of acromegaly the anatomical and radiological studies of the skeleton reveal a diffuse dense sclerosis which fills in the previously over*expanded cancellous bone* *This secondary manifestation of hypophysial in*sufficiency contributes to the massive thickening of the skull and other parts of

the bouts of transient hyperthyroidism or diabetes mellitus which are encountered so commonly The association of a compelling polyphagia and obesity are consistent, however, with a hypothalamic disturbance, which could be secondary to the pressure effects of an expanding hypophysial tumor A third possibility is suggested by the observations of Lee[11], who found that the administration to rats of an adenohypophysial growth hormone increased the appetite and the voluntary food consumption and promoted weight gain by an increased deposition of body protein The fact that hormones such as estrogens, progesterone and pitressin, are known to affect the function of certain hypothalamic centers suggests that the second and third of these possibilities may have a common denominator, i e the growth hormone elicits its effect on appetite and body weight by way of the hypothalamus

Differential Diagnosis

The nature of the disease process in the fully developed syndrome is identified easily by the general appearance of the patient and confirmed by x ray examination of the sella turcica sinuses mandible, general configuration of the skull and terminal phalanges Diagnostic difficulties are more apt to arise in the recognition of the so called fugitive cases and of the very early or very late phases of this disease

The early stages of acromegaly frequently are confused with other conditions Rheumatoid pains may suggest arthritis or in the absence of objective physical findings the combination of vague muscle and bone pains, nervousness, weakness and insomnia often lead to a diagnosis of hypochondriasis The significance of the headache is quite apt to be misinterpreted The acroparesthesias and burning sensations of the hands may suggest syringomyelia Early disturbances in gonadal function particularly with the onset of amenorrhea are especially misleading The relatively frequent complication of acromegaly by hyperthyroidism, diabetes mellitus diabetes insipidus and the hypothalamic syndrome, which is characterized by polyphagia obesity and hypersomnolence, may direct attention for a time from the primary hypophysial disease to one or more of these secondary clinical disorders The cutaneous hyperpigmentation weakness vague gastro intestinal symptoms and hypotension may suggest an early phase of Addison s disease The otolaryngologist not too rarely has treated an early case of acromegaly for chronic upper respiratory disease and sinus disease without recognizing the significance of the periodic, often blood tinged, nasopharyngeal, mucoid discharges The ophthalmologist who is confronted by an unexplained diplopia, should search for homonymous hemichromatopsia since it precedes the development of a full blown hemianopsia

The discovery of a tumor in the region of the sella with incipient optic atrophy

in a patient whose symptoms are somewhat obscure presents the clinician with a diagnostic problem of some moment The differential diagnosis must be made preoperatively in order to determine upon the proper course of therapy For instance the acidophilic adenomata are quite sensitive to roentgen therapy whereas the chromophobe tumors are much less so Aneurysm of the chiasmal area at times closely resembles hypophysial adenoma because it may produce great enlargement of the sella optic atrophy and visual field defects Aneurysm may be differentiated from other chiasmal tumors by x ray examination which may show a characteristic crescentic shadow from calcification in its wall or by arteriograms taken during the injection of thorotrast into the common carotid artery Naturally they call for a special form of therapy

The group of tumors consisting of chiasmal gliomas suprasellar meningiomas and cholesteatomas or chordomas should be recognized preoperatively so that there may be intelligent preparation for the special problems involved in their excision Any of these tumors by virtue of their anatomical location may be confused with acidophilic adenomata because they produce the same neighborhood signs and symptoms as a result of pressure upon the optic nerves and hypothalamus With the exception of the craniopharyngiomas which interfere with rather than accelerate growth and the chromophobe adenomata which affect adenohypophysial function by pressure atrophy the other masses usually do not induce hypophysial dysfunction Furthermore the craniopharyngiomas generally are cystic and give x ray evidence of calcification above the sella and the latter while deformed is not often symmetrically distended as in the case of the hypophysial adenomas Moreover these cysts tend to grow posterior to the chiasm in the direction of the third ventricle where their pressure produces an internal hydrocephalus with generalized increased intracranial pressure and choked discs instead of primary optic atrophy

The meningiomas in contrast to the craniopharyngiomas are found almost exclusively in adults although either tumor may occur in both age groups The meningiomas generally produce optic atrophy and bitemporal hemianopsia but the sella is likely to be normal in size or only slightly deformed The wide sellar expansion characteristic of adenomas ordinarily is not seen in connection with gliomas of the optic chiasm and nerves cholesteatomas and chordomas Although optic atrophy usually is present the visual field defects take unexpected forms and evidence of endocrine dysfunction rarely is well marked and usually limited to the hypothalamus

In the late phases of acromegaly the anatomical and radiological studies of the skeleton reveal a diffuse dense sclerosis which fills in the previously over expanded cancellous bone This secondary manifestation of hypophysial insufficiency contributes to the massive thickening of the skull and other parts of

the skeleton As a result of these late changes acromegaly may have to be differentiated occasionally from leontiasis ossea, Paget s disease and Marie s hypertrophic pulmonary osteoarthropathy In the latter condition the skull remains unaffected although the nose may appear prominent, the finger tips are clubbed, and the hands and feet increase but slightly in size The kyphosis is thoracolumbar whereas in acromegaly it is cervicodorsal The enlargement of the hands and feet in osteoarthropathy is, on rare occasions sufficient to cause some temporary confusion with acromegaly but the rest of the clinical picture should distinguish the one from the other Paget s osteitis deformans scarcely is likely to be mistaken for acromegaly The cranium is enlarged, chiefly in circumference the long bones are pathologically bowed, and the asymmetrical skeletal changes show characteristic roentgen changes in the skull and long bones

Treatment

The type of therapy which is instituted in acromegaly, is dictated in large measure by considerations which arise in the individual case There are three therapeutic procedures which are available viz x ray therapy, surgery and use of hormones

X Ray Therapy — In 1909 Gramegna reported the first case of acromegaly with hypophysial tumor to be treated by roentgen rays[110] Since that time the majority of reports have indicated that irradiation is of much benefit in many cases[108, 109, 110, 111, 11, 113, 114, 115, 116, 117, 118, 119] Most of these observers favor irradiation as the method of choice in the treatment of hypophysial adenomata uncomplicated by advanced involvement of the optic chiasm and nerves The ideal patient for roentgen therapy is one who has endocrine disturbances and possibly a slight enlargement of the sella turcica but no visual disorders It is patently unwise to await development of the latter before instituting treatment

Heinismann and Czerny[108] confirmed by Dyke and Hare[1 9] have pointed out that the acidophile adenomas in acromegaly respond to irradiation better than the chromophobe type Judging from the various reports roentgen therapy has induced improvement in visual acuity, headache and secondary endocrine disorders for a period of from 1 to 7 years or more in many patients Even if vision is unimproved by x ray therapy its progressive deterioration may be halted for many years[109] There is general agreement particularly emphasized by Dott Bailey and Cushing[113] that roentgenotherapy should be followed by carefully controlled and frequent perimetric observations, and that surgical intervention is indicated, if vision continues to diminish

Radiation apparently causes a temporary regression of vision for 24 hours after the treatment is administered[1 9] This may be due to post radiation edema of the

tumor and adjacent brain tissue since the vision usually begins to improve within 12 to 24 hours after these initial undesirable effects are noted

Failure to achieve improvement with roentgenotherapy may be due to an irreparably damaged optic chiasm and nerves or the hypophysial tumor may be largely cystic and consequently unresponsive

The amount of radiation needed appears to vary from case to case Dyke and Hare [2] have noted improvement in vision headache lethargy and other general symptoms after several hundred roentgen units Other cases did not respond until 2 000 r to 4 000 r had been given They suggest therefore that therapy be continued provided that vision is not too greatly diminished until the patient has received three or four series of treatments each of which consists of a total of 2 400 r to each of three portals

Surgery — Endocrine disorders alone without evidence of pressure upon the optic nerves optic chiasm or the hypothalamic structures rarely if ever justify surgery of the hypophysis Loss of vision from optic atrophy and symptoms of increased intracranial pressure produced by adenomas which extend backward and upward constitute the only clear cut indications for reducing the size of the tumor or for its complete removal [0]

The sella turcica was approached surgically first through the nasal accessory sinuses since the deeper of these structures lies beneath the hypophysial fossa In 1906 Schloffer operated upon a hypophysial tumor through an extensive resection of the endonasal and postnasal structures including the ethmoid and sphenoid cells This original procedure was employed and subjected to simplifying modifications by Hochenegg [9] and von Eiselsberg[1] [1] in 1907 by Kanavel [4] Hirsch [9] Kocher[1] and Lecene[1] in 1909 and by Halstead in 1910 An account of the degree to which Cushing perfected this operative approach may be gathered from his monograph in 1912 and his two subsequent reports in 1914[1] [3] and 1922[1]

In Hochenegg s first two cases of acromegaly and in one of O Hirsch s patients there were unmistakable signs of post operative subjective and objective improvement The rheumatoid pains disappeared the acra decreased in size the menses were restored and recurred at regular intervals the skin became softer and the excessive hairiness regressed These observations have been confirmed repeatedly especially by Cushing

According to Horrax the operation of choice at this time is the transfrontal intracranial approach Modern advances in technical skill have lowered the operative mortality of this procedure from its previously prohibitive levels [3] [13] [132] to less than 5 per cent The hypophysial tumor is more accessible it can be evacuated more completely and vision is more likely to be improved or restored by this method than by the transphenoidal technic Cushing[1] [3] states whereas

37 per cent of the patients after transphenoidal operations and 42 per cent after transfrontal operations showed considerable or marked improvement in vision, only 9 per cent of the transphenoidal operations in contrast to 21 per cent of the transfrontal operations were followed by restoration of the visual field and acuity essentially to normal

Hormone Therapy — Endocrine therapy in acromegaly has two aims, either to induce regression of the acidophilic pathologic process, or to correct the endocrine disorders secondary to adenohypophysial insufficiency The former, which still is wholly in its experimental stage is based on experimental evidence, which indicates that the sex hormones have a depressant effect upon certain aspects of adenohypophysial function It is difficult however, to envisage success in this connection, where a growing tumor is concerned whereas an uncomplicated hyperplasia of the acidophiles might be a more logical target for this form of therapy

Substitution therapy for the repair of disabilities resulting from adenohypophysial insufficiency is also in its developmental stages, principally because a clinically satisfactory extract of all the principles of the adenohypophysis is not yet available Contrary to the therapeutic indications in Simmonds disease such an extract should contain all factors except that concerned with growth, if it is to be used in the treatment of this phase of acromegaly Whether or not this omission would limit or in some way modify the clinical activity of the extract remains to be seen Nevertheless much can be done to obviate the secondary manifestations of genital adrenal thyroid and posterior lobe deficiencies Nature herself fortuitously has taken a hand in the management of the diabetes mellitus, inasmuch as the advent of adenohypophysial insufficiency generally heralds a change from a state of decreased to one of increased carbohydrate tolerance The other deficiencies are treated in the orthodox fashion with the possible exception of that of the thyroid It has been pointed out[13, 14, 15] that thyroid therapy in such circumstances may precipitate an acute attack of adrenal insufficiency by virtue of the sudden excretion of sodium chloride and water in an individual whose adrenal cortex already is significantly atrophied The likelihood of such an accident in a patient who needs thyroid therapy furnishes a clear cut indication for the combined administration of thyroid sodium chloride and possibly adrenocortical extract

Giantism

Definition

Giantism may be defined as an anomaly of skeletal growth characterized principally by a stature which is considerably in excess of the average measure

ments of individuals of the same race. Associated with this general symmetrical *overgrowth of the body there is usually a decided impairment in sexual functions* and persistence of ununited epiphyses.

Biological Significance

It is customary to refer to the various bony skeletal findings in giantism as pathognomonic of this disease but Launois and Roy[136] believe that these are merely exaggerations of the conditions found in normal men who are unusually tall. Thus in order to understand the atypical growth of giants it is essential to recall the laws and progress of normal growth. To merit the title of giant it is not sufficient for an individual merely to be extraordinarily tall. Of two persons of equal height one may be a giant and the other a normal but unusually tall individual. There are no sharply defined differences between the normally tall man and the giant. The one merges into the other through a wide variety of in between types. Individual variability is almost endless. This applies to the height as well as to the proportions of the various parts of the body. The body type varies with race, country, diet, quantity and form of muscular activity, etc.

Launois and Roy have concluded that the same laws which govern the growth of so-called normal individuals determine the type of overgrowth which occurs in giantism[136]. They find for the giant, as did Godin[137] for the normal, that the growth drive continues at irregular intervals which are interrupted by periods of relative slowing.

The genetic factors which Stockard[138,139] observed and demonstrated for the pathogenesis of acromegaly in various breeds of dogs are equally applicable to the disorder of growth in giantism. It is likely that in giantism, just as in acromegaly, the individual inherits a constitution, which is expressed in terms of a genetically determined defect in the structure and function of the adenohypophysis. Eunuchoidal characteristics may or may not be a feature of this constitutional deviation from the average normal growth, a matter which has been discussed recently by Mansbacher[140]. The latter has suggested that the eunuchoidism may be a familial characteristic in much the same way as the giantism with which it is associated often.

Incidence

Giantism is a relatively rare condition. Its incidence apparently is greater in the male than in the female. Of 14 accurately studied cases which were reviewed by Hutchinson[141,142] 10 were in males. Examples of familial giantism may be more common than the number of recorded cases indicated. In his studies

of inheritance of stature Davenport[143] has collected data on a few families distinguished by unusually tall members One reason for the dearth of statistics on this phase of the subject may be the difficulty in differentiating the various clinical types of linear overgrowth Most giants exhibit infantilistic or eunuchoid characteristics which must be differentiated from the gonadal hypoplasia associated with so called secondary eunuchoidal giantism

Pathology

The pathological material, upon which studies of giantism have been based, is limited in amount but has been examined carefully Hutchinson[141,14] reported 3 cases in all of which the adenohypophysis was found to be considerably enlarged by a neoplasm Launois and Roy[146] collected a larger series of autopsied cases which disclosed that an adenoma of the adenohypophysis was present in all true giants whereas only hyperplastic enlargement of the gland occurred in other instances of unusually tall stature e g eunuchoidal overgrowth The available evidence indicates that all such adenohypophysial tumors consist of acidophilic cells, and that the acidophiles are affected also in cases of hyperplastic enlargement of this gland Consequently it is believed that the pathological process which induces giantism is responsible also for the development of acromegaly[1,6,141,14,144,145] As was noted elsewhere in this chapter the acidophilic tumor probably induces giantism if it affects the growth of an individual prior to union of the epiphyses, and acromegaly results if the adenoma becomes active after epiphyseal union A variable mixture of these two clinical states occurs, if the pathological process spans the period of adolescence and adulthood

These conclusions are of interest in view of Rasmussen's observations[148], which fail to show any correlation between the percentage of acidophiles and stature Roessle[14,14] Petersilie[149] and Rasmussen[148] have found, however that there is a distinct positive correlation between body length and the weight of the entire hypophysis Rasmussen s studies[148] have disclosed also a moderate degree of positive correlation between stature and the weight of the pars distalis

Clinical Course

Since the growth curve of the giant is essentially an exaggeration of the normal according to Launois and Roy[1,6] it is not surprising that the abnormal growth of giantism ordinarily begins during the periods of accelerated growth in normal children Although the earliest evidence of giantism is encountered during the first year of life Biedl reported that most cases become clinically apparent late in childhood, usually at the time of puberty[150] A classical example of the infant

giant occurred in the Alton boy who began to grow excessively soon after birth[151] By the time he was 2 years of age his height arrested attention and at 9 he measured over 6 feet in height By his twelfth birthday he had grown to almost 7 feet and at 18 he topped the extraordinary height of 8 feet 3 inches The stature of verified cases on record varies from 7 feet 6 inches to 8 feet 6 inches in the case of the famous giant in Trinity College Dublin A fantastic height of 9 feet or more has been claimed for various human giants but Roessle states that these are not authentic measurements[1 7 148]

An extensive survey of approximately 100 cases of giantism indicates that the life of these unfortunates is short and far from merry Dana has found[16] that the average length of life is 21 3 years although some of these individuals lived beyond 50 years of age The end of life generally is heralded by a diminishing vitality and the immediate cause of death usually is a mild intercurrent infection which in other circumstances would be of no clinical significance

Launois and Roy[128] point out that the epiphyses of giants remain ununited many years beyond the period of normal ossification The giant continues to grow in height as long as this prepuberal condition of the growth cartilages persists The clinical stigmata of acromegaly generally are inconspicuous in the growing giant but emerge as part of the syndrome when the growth period has terminated *because the fundamental pathology of both diseases is the same* Thus a considerable proportion of giants become acromegalic in adult life

Physical Signs and Symptoms

Contrary to popular belief giants in size are not supermen in strength Cases have been reported *in which unusual physical prowess was a passing phase early* in the course of this malady For the most part however giants are physically weak and have difficulty in supporting their weight safely[141 142] A survey of the literature also discloses that *the majority of giants are indolent and fail to develop* an intelligence much beyond that of a child s and failure of memory is a common complaint Hutchinson [1 5] believes that giants are feeble minded because of their disease *It is also possible that their freakish overgrowth interferes* seriously with their social and psychological adjustments and their progress in educational pursuits

Most giants suffer from a decided impairment in sexual functions but this is not invariably characteristic Entirely normal or even exaggerated sexual development in the early phases of this disease is not inconsistent with the diagnosis Although many of these individuals have been urged into wedlock by business managers in the belief that they would reproduce their kind their marriages have been few and largely infertile The external genitalia have been found to be

markedly underdeveloped in most of the cases in which trustworthy observations have been made In Hutchinson s case of female giantism the uterus was infantile, the ovaries rudimentary and the clitoris markedly hypertrophied

The abnormal stature of giantism is associated with certain characteristic bony changes, among the most prominent of which is the overgrowth of cancellous bone throughout the skeleton The mastoid cells and sinuses become extraordinarily large in size and the squamous portion of the temporal bone is hyperpneumatized The broad diploe between the inner and outer tables of the cranium are unusually prominent The characteristic physiognomy and prognathism of the giant is due in large part to the facial bones and particularly, to the mandible, which is hyperpneumatized

Relatively narrow shoulders have been encountered in many of the larger giants Thus the height span relations are affected and become an important index to a characteristic feature of giantism The span usually measures less than the total height because of the narrow width of the shoulders During his twelfth year the Alton giant grew 11 cm in height, increased 11 5 cm in arm span and 13 cm in circumference at the level of his iliac crest, but the length of the clavicles remained stationary[153]

The abnormally long arms hang beside the giant in simian fashion Giants have enormous feet and characteristically enlarged, spade shaped hands Both jaws are hugely developed the cheek bones are extremely prominent, and the supraorbital ridges project to such a degree that they resemble those of an anthropoid ape

Differential Diagnosis

Constitutional Statural Overgrowth — The excessive growth of giantism differs from the normal physiological development only in that the length of the extremities and body height and the size of the viscera are considerably in excess of the average measurements peculiar to the race of the individual concerned A height of over 6 feet is not considered gigantic among members of the Scandinavian peoples, whereas the same stature in an individual of one of the Latin races might well raise the question of hypophysial dysfunction In addition to race height is influenced also to a considerable degree by genetic factors Excessive stature may be essentially an inherited characteristic which is dependent upon genetic constitution In such instances neither the skeleton nor the other organs of the body exhibit any evidence of disease (Fig 28) It should be noted, however, that a genetically determined tall stature in one or both parents does not rule out the possibility of a pathological overgrowth, if one of the offspring also develops excessively In such circumstances the possibility of abnormal growth

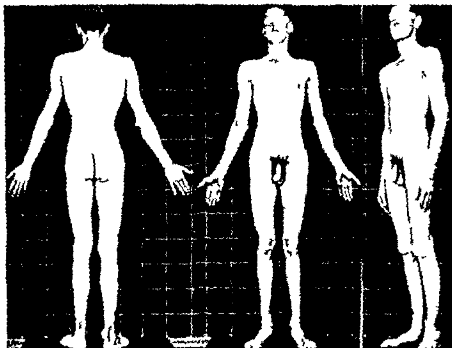


FIG 8 Constitutional statural overgrowth Age 18 Sella turcica small measuring 5 x 7 mm with partial convergence of clinoid processes Bones of hands and wrists are unusually large and the ulnar epiphyses are not completely fused No family history of giantism but one sister aged 20 grew 2 inches within a few months after giving birth to a baby and a paternal aunt grew several inches rapidly after she was 20 years of age Father is [illegible] inches tall mother 61 inches Patient weighs 163 pounds and is 77¼ inches in height Lower skeletal segment 42⅞ inches Upper skeletal segment 34⅜ inches Arm span 79⅜ inches The eunuchoidal skeletal measurements are associated with virtual absence of body hair transverse pubescence poor libido and unusually small prostate It is difficult to explain the normal size of the external genitalia unless one assumes that the development of the penis and gonads is a genetic variation which is not an expression of the state of gonadal function Note prominent mandible which has not resulted in malocclusion in this case Reproduced through the courtesy of E Kost Shelton M D

should be investigated whenever children or adolescents are oversized for their age or begin growing at too rapid a pace

Eunuchoidal Giantism — Statural overgrowth associated with primary gonadal hypoplasia must be differentiated from true giantism which also is characterized commonly by undeveloped genital organs Both conditions exhibit a somewhat similar general appearance and skeletal configuration, but there are

several distinguishing features which aid in the differential diagnosis (Fig 29) X ray examination of the phalanges of the eunuchoidal giant shows a more slender, less massive bone structure than is characteristic of the true giant Furthermore, the skeletal measurements are more disproportionate in the eunuchoidal individual, whose span may be considerably in excess of his total height, whereas the span of the true giant ordinarily is equal to, or shorter than, his total height The latter may be attributed to the failure of his clavicles to grow in proportion to the rest of the skeleton This results in narrow shoulders and shortens the span, which might exceed the total height otherwise Finally, roentgen study of the sella turcica may disclose a small fully enclosed bony structure in the case of the eunuchoid giant whereas an enlarged, eroded sella turcica is found ordinarily in the true giant It should be emphasized, however, that the absence of a pathologically altered sella turcica does not necessarily distinguish the one from the other in puzzling diagnostic problems The author has observed one case and Hurxthal and Horrax[14] have reported another in which the development of giantism was traced to a verified hypophysial tumor, although roentgen evidence of an enlarged sella turcica was lacking A pneumoventriculogram may disclose the diagnosis in these circumstances because the expanding tumor, which has herniated through a frail diaphragma sellae, often produces a filling defect in, and a displacement of the ventricular system Involvement of the optic chiasm or optic nerves occurs ordinarily in such cases and aids thus in the differential diagnosis Delayed union of the epiphyses occurs in both types of statural overgrowth under consideration, so that this finding does not help in differentiating these conditions

Statural Overgrowth in Exophthalmic Goiter — The rate of growth is accelerated in juvenile and adolescent individuals who are afflicted with exophthalmic goiter during the period of their active growth[155,156,157,158,159,160,161] Consequently such individuals are taller than average for their age, sex and race The duration of this accelerated rate of growth is not a factor in the final unusual height which is attained inasmuch as the epiphyses unite at the proper time There should be no difficulty in the differential diagnosis of this condition from that of true giantism even though a height in excess of 6 feet may be attained rapidly in occasional instances As a matter of fact the clinical problem, with which one is confronted in such cases stems generally from anxiety over the unusual rate of growth in a child that lacks emotional stability

Urinary Excretion of Hormones in Relation to Problems of Growth — Individuals exhibiting eunuchoidal giantism due to primary gonadal failure excrete an increased amount of FSH and a decreased amount of the estrogenic and androgenic hormones in the urine The neutral 17 ketosteroid excretion may be within normal limits or moderately decreased The author is

Fig 29 Eunuchoidal gigantism in a 15 year old boy Note disproportionate skeletal measurements cubitus valgus extreme hypoplasia of external genitalia Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital.



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occur in the male Tumors of the sex glands have been reported in both sexes but tumors of the pineal are sex linked and occur exclusively in the male

Treatment

Of the various forms of therapy which have been suggested for the control of excessive growth in primary hypophysial giantism none is advocated with enthusiasm Horrax[1] states that surgical removal of the acidophilic tumor which is associated commonly with this condition is indicated only rarely since visual disturbances are infrequent and roentgenotherapy often arrests the growth of expanding acidophile tumors of the adenohypophysis Surgery appears to be the method of choice only when radiation fails to produce significant improvement in the eyesight of individuals who develop optic atrophy

Androgenic and estrogenic hormone therapy has been advocated in recent years[63 164] for the control of eunuchoidal giantism in the belief that these substances either depress adenohypophysial function or initiate rapid union of the epiphyses Although apparent success has been achieved in a few cases it is difficult to judge the accuracy of such observations inasmuch as the rate and extent of statural growth may vary spontaneously and abruptly in a given individual without reference to the therapy which has been administered It was indicated in a previous section of this chapter that the androgens of the adrenal cortex may be involved in initiating union of the epiphyses and cessation of growth Whether or not the androgenic corticosteroids behave differently in this respect from the androgens derived from the testes is still to be determined If substantiated the information may have significant therapeutic implications

The discussion of hormone therapy in acromegaly contains a statement of the present views on that phase of the subject as it relates to acidophilic tumors and hyperplasia of the adenohypophysis Because of the similarity in pathology presumably much the same indications and limitations apply to the use of this form of therapy in giantism

Dwarfism

Definition

A dwarf is an individual whose physical dimensions are considerably below those characteristic of his age group sex and race The term *dwarfism* per se refers to the diminutive stature and may be due to one or more of many causes such as genetic variation secondary to germinal defects adenohypophysial deficiency secondary to various types of tumor in the hypothalamo hypophysial area congenital or acquired hypothyroidism hypophysial neighborhood or sys

not aware of similar studies on hypophysial giants Klinefelter, Albright and Griswold[16] have studied the FSH excretion in patients with acromegaly, however Since these two syndromes are associated with the same pathological lesion of the adenohypophysis it is of interest to note that the excretion of FSH may be normal decreased or elevated in acromegaly Presumably the level of excretion depends in large measure on the extent to which the expanding acidophilic tumor damages the basophilic cells through pressure atrophy In one case of acromegaly which occurred during the menopause, the FSH excretion was found to be increased[16] In the author s experience the 17 ketosteroid excretion is normal, decreased or virtually absent in acromegaly The amount of excretion parallels closely the clinical activity of the acromegalic process The 17 ketosteroid excretion is normal in early well established cases, decreased in moderately advanced states and absent in individuals who show clinical evidence of hypophysial deficiencies secondary to local destruction of the functional adenohypophysial parenchyma

Rare Childhood Disorders of Growth and Sexual Development —The hypophysial type of overgrowth is not characterized by sexual precocity, which ordinarily signifies disease of the gonads, of the adrenal cortex or of the pineal body, nor do these non hypophysial types of overgrowth end in giantism This comparatively rare group of childhood disorders of growth and sexual development are included under the general heading of *macrogenitosomia praecox* As the name indicates the salient features of these conditions are precocious skeletal somatic and genital development Ossification centers appear too early bone development is advanced correspondingly, and epiphyseal union takes place prematurely Although such children seem remarkably overgrown when they come under observation they do not exhibit giantism in adult life As a matter of fact, the reverse is true of those who survive to adulthood Such children are dwarfed because premature closure of the epiphyses and early maturation of the reproductive system result in cessation of longitudinal growth long before it should occur normally

More often these patients do not survive their childhood, because the pathological condition responsible for their precocious development is a malignant tumor of the adrenal cortex, pineal or gonads Friedgood and Gargill[1] have observed an instance of malignant adrenocortical tumor in an 8 year old girl, who showed skeletal and somatic precocity and menstruated for six months before she developed outspoken virilism associated with amenorrhoea The condition is found more commonly in female children who develop the symptoms and signs of virilism Boys who are affected by a similar neoplasm develop premature over masculinization Neoplasms of the gonads induce menstruation at an early age in the female whereas priapism and spermatogenesis

it is generally believed that the Lorain dwarf has the body proportions of an adult in miniature. There is nothing in the Lorain Faneau de la Cour treatise to justify this interpretation. Actually what they stated was that their tuberculous patients, both male and female, were juvenile in appearance and persistently infantile in somatic and sexual development despite advancing years. They reported that a fragile body habitus, spindly limbs, small bones and weakness were the outstanding characteristics of an arrested somatic development which affected the whole body rather than any special part of it. The teeth of these adult dwarfs were mostly of the first dentition. The breasts of the women were undeveloped, they had little or no axillary or pubic hair, and although their external genitalia were of the female type they were immaturely developed. In the absence of autopsy or x ray data Faneau de la Cour surmised that their epiphyses were ununited, a remarkably accurate deduction in the light of subsequent more modern studies. The secondary sexual characteristics of the tuberculous males affected by this condition were predominantly feminism and the development of their external genitalia seriously arrested. They had broad hips, absence of hair on face and thorax, long eyelashes, prominent breasts, fine silky hair of the head, small testes and an infantile penis. For example the development of the external genitalia in one of their cases, a man of 25, was equivalent to that of a child of 8 or 9 years.

It would scarcely serve any useful purpose to recapitulate the tedious academic arguments which cluttered the literature on this subject subsequent to the Lorain Faneau de la Cour article. Some of it may be gotten from papers by Brissaud and Meige and Bauer[26] who contributed to the controversies regarding relative body proportions and etiological factors in infantilism. In 1908 Levi described an instance of infantilistic dwarfism in which an hypophysial tumor was obviously the primary pathological lesion[1, 9, 17a, 17]. The literature which accumulated after this report refers repeatedly to the Lorain Levi syndrome. So far as this writer can determine the clinical characteristics of these two groups of infantilistic dwarfs are essentially identical. From this viewpoint there appears to be some justification for the syndrome's name. Etiologically, however, they are unrelated, the Lorain Faneau de la Cour syndrome having been found in association with pulmonary tuberculosis, whereas Levi's case was due to a destructive lesion of the adenohypophysis.

The most widely quoted classification of dwarfs was introduced by von Hansemann[27] in 1902. His disproportioned dwarfs included the rachitic, achondroplastic, kyphoscoliotic and cretinoid forms, and the well proportioned dwarfs were subdivided into primordial and infantile types. The primordial dwarfs are of normal intelligence and in the absence of evidence to the contrary may be considered as examples of a disordered growth which results from defects in germ plasm. They are abnormally small at birth and although their rate of growth

temic infections severe nutritional deficiencies and chronic heart disease acquired congenitally or in infancy The association of gonadal hypoplasia with dwarfism of whatever cause is termed *infantilism*

Hypophysial dwarfism is a chronic endocrine or neuroendocrine disorder which is characterized in the large majority of cases by adenohypophysial pathology during the period of somatic development This form of dwarfism is recognized clinically by a well proportioned diminutive infantile stature and a correspondingly small head with child like features which acquire an incon gruous wizened oldish expression relatively early in life Union of the epiph yses is delayed markedly or never occurs, but it may be encountered in those hypophysial dwarfs who mature sexually in rare instances Among the various infantile characteristics which persist in hypophysial dwarfs, is under development or atrophy of the genital apparatus and emotional immaturity *Hypophysial infantilism* is characterized furthermore, by certain biochemical and biological changes including markedly reduced or absent urinary excretion of neutral 17 ketosteroids and urinary gonadotropin abnormal sensitivity to injec tions of insulin and an increased tolerance for carbohydrates

Historical Background

Numerous examples of skeletal dwarfism associated with gonadal hypoplasia have been recorded in the medical literature Considerable confusion has re sulted from attempts to separate them into well defined clinical syndromes, be cause in many instances etiological factors have been essentially obscure, dis tinctions between groups of cases are not hard and fast and intermediate forms of this disorder have defied all efforts at logical classification Particularly dif ficult has been the task of differentiating between hypophysial dwarfism and the stunted stature which appears to be due to a genetic modification of growth based on germinal defects To further complicate the situation there have been numer ous relatively unimportant and involved academic controversies on matters of terminology Reference to Falta s involved analysis of the arguments and counter arguments on various aspects of infantilism gives some idea of this unsat isfactory state of affairs[165]

In 1871 Lorain and Faneau de la Cour[166] described a group of tuberculous individuals in whom they noted arrested skeletal and genital development They termed the condition infantilism Unfortunately a misquoted version of their paper was incorporated into the literature on dwarfism and infantilism, and Lorain s name was identified with a syndrome which was not precisely what he and his pupil described The confusion in terminology and the pointless academic discussions which have centered about the error are a matter of record Briefly

it is generally believed that the Lorain dwarf has the body proportions of an adult in miniature There is nothing in the Lorain Faneau de la Cour treatise to justify this interpretation Actually what they stated was that their tuberculous patients both male and female were juvenile in appearance and persistently infantile in somatic and sexual development despite advancing years They reported that a fragile body habitus spindly limbs small bones and weakness were the outstanding characteristics of an arrested somatic development which affected the whole body rather than any special part of it The teeth of these adult dwarfs were mostly of the first dentition The breasts of the women were undeveloped they had little or no axillary or pubic hair and although their external genitalia were of the female type they were immaturely developed In the absence of autopsy or x ray data Faneau de la Cour surmised that their epiphyses were ununited a remarkably accurate deduction in the light of subsequent more modern studies The secondary sexual characteristics of the tuberculous males affected by this condition were predominantly feminism and the development of their external genitalia seriously arrested They had broad hips absence of hair on face and thorax long eyelashes prominent breasts fine silky hair of the head small testes and an infantile penis For example the development of the external genitalia in one of their cases a man of 25 was equivalent to that of a child of 8 or 9 years

It would scarcely serve any useful purpose to recapitulate the tedious academic arguments which cluttered the literature on this subject subsequent to the Lorain Faneau de la Cour article Some of it may be gotten from papers by Brissaud[167] and Meige and Bauer[168] who contributed to the controversies regarding relative body proportions and etiological factors in infantilism In 1908 Levi described an instance of infantilistic dwarfism in which an hypophysial tumor was obviously the primary pathological lesion[16, 170, 171] The literature which accumulated after this report refers repeatedly to the Lorain Levi syndrome So far as this writer can determine the clinical characteristics of these two groups of infantilistic dwarfs are essentially identical From this viewpoint there appears to be some justification for the syndrome s name Etiologically however they are unrelated the Lorain Faneau de la Cour syndrome having been found in association with pulmonary tuberculosis whereas Levi s case was due to a destructive lesion of the adenohypophysis

The most widely quoted classification of dwarfs was introduced by von Hansemann[17] in 1902 His disproportioned dwarfs included the rachitic achondroplastic kyphoscoliotic and cretinoid forms and the well proportioned dwarfs were subdivided into primordial and infantile types The primordial dwarfs are of normal intelligence and in the absence of evidence to the contrary may be considered as examples of a disordered growth which results from defects in germ plasm They are abnormally small at birth and although their rate of growth

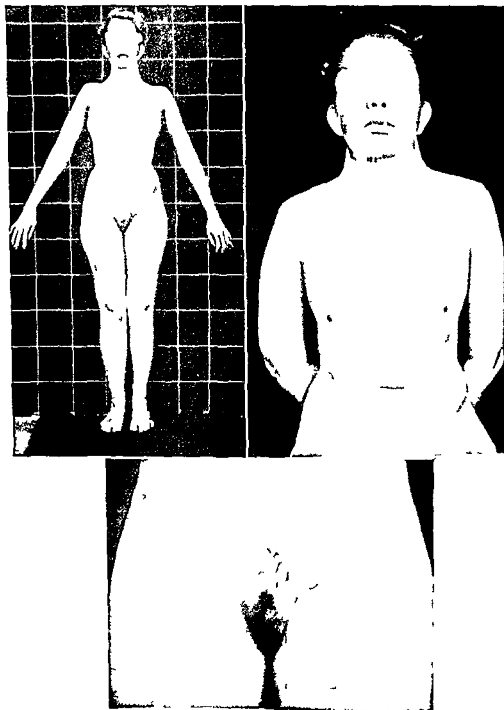


Fig 30 Turner's syndrome in a 25 year old girl with primary amenorrhoea Note webbed neck absence of breast development and hypoplasia of genitalia Compare with similar case in Fig 31 in which dwarfism is a factor Courtesy of E Kost Shelton M D

remains inhibited the epiphyses unite at the usual time They mature sexually and develop secondary sexual characteristics at puberty at the expected time Many of these individuals are capable of procreation and may have normal children The infantile dwarfs who are brought about by adenohypophysial deficiency are normal in size or somewhat smaller than normal at birth At some later time usually in early childhood their growth ceases entirely or is retarded so that the rate of growth is interfered with seriously The epiphyses remain ununited indefinitely development of the primary and secondary sexual characteristics either fails entirely or is significantly impaired the intellect sometimes remains puerile but is not defective Von Hansemann s infantile dwarf obviously is identical with Gilford s[1, 3] asexual ateleiotic dwarf and with the Paltouf type of dwarfism[174] whereas von Hansemann s primordial dwarf corresponds to Gilford s sexual ateleiotic dwarf[1] Sternberg[1, 6] who believed that infantilistic dwarfism sometimes is due to primary gonadal hypoplasia further subdivided von Hansemann s class of infantile dwarfs into hypophysial and hypoplastic gonadal types The association of stunted growth with agenesis or arrested development of the ovaries has been recognized pathologically and described by Olivet[177] Sellheim[1, 8] Randerath[17] Schurmann[1] Pela[183] Priesel[8] Rossle[183] Goldwasser[184] Tronci[185] Sharpey Shafer[1, 6] and Walkins and Fleischmann[187] Various clinical aspects of this syndrome were reported in detail by Turner[2, 8] Varney Kenyon and Koch[9] Albright Fraser and Smith[190] Schneider and McCullagh[1] and Wilkins and Fleischmann[19] Sometimes it is called Turner s syndrome (Figs 30 and 31) It is characterized by a dwarfed stature and retarded or absent sexual development in association with high titers of urinary gonadotropin and an abnormally low excretion of androgens and estrogens The external and internal genitalia are infantile development of the breasts is lacking and there are small to moderate amounts of axillary and pubic hair in spite of a complete lack of the other so called secondary sex characteristics Menses occur only infrequently and usually not at all depending on the extent to which the ovarian development is arrested Congenital anomalies such as webbing of the neck and short neck in association with abnormalities and fusion of the cervical vertebrae and cervical spina bifida are encountered not infrequently Other congenital anomalies which have been noted include squint bilateral ptosis bilateral cataracts tubular vision lack of retinal pigment deafness and mental retardation Individuals who comprise this group may or may not be obese and examination of their photographs[18] discloses that usually they have the body proportions of a child although eunuchoidal skeletal measurements have been observed[87, 12, 1] It is thought that the association of growth and ovarian defects may be of genetic rather than of physiological significance[187, 9, 19] The differentiation of these cases from those of hypophysial origin has been undertaken in a subsequent section of

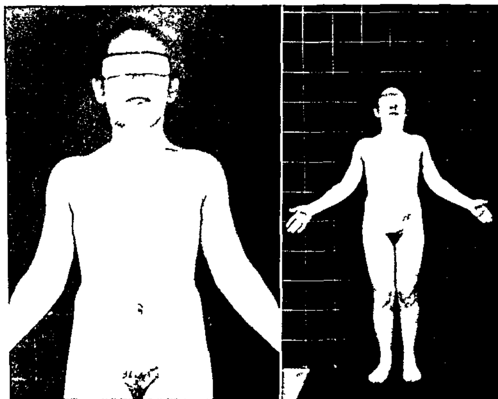


Fig 31 Turner's syndrome in a 19 year old girl with primary amenorrhoea Note webbed neck absence of breast development cubitus valgus and dwarfism Reproduced through the courtesy of E Kost Shelton M D

this chapter In a recent critical review of the many clinical aspects of dwarfing Shelton[193] has suggested the following classification of dwarfism and infantilism from a practical viewpoint

(1) Inherent or constitutional factors as in so called primordial dwarfism and in normal small statured persons

(2) Congenital disturbances of the skeleton as in achondroplasia mongolism and micromelic dwarfism

(3) Anomalies of the circulatory and urinary systems as in congenital heart and kidney disease angioplastic infantilism and renal rickets

(4) Disturbances of nutrition

(a) Inadequate food vitamin and mineral intake, as in slow starvation rickets and other deficiency diseases

(b) Inadequate absorption of the building essentials because of disturbances

of the gastric intestinal and pancreatic enzymes as in hypochlorhydria celiac disease refractory rickets and intestinal nematodes

(c) Inadequate utilization or deposition of the essential elements because of various metabolic and endocrine disorders as hypothyroidism hypopituitarism and diabetes mellitus

(5) Chronic infectious disorders as in tuberculosis and syphilis

Pathology

There are relatively few recorded data of autopsies on dwarfs So far as this writer can ascertain all such observations have been made on infantilistic dwarfs none are available for the so-called primordial dwarf The adenohypophysis was found affected in some way in each instance The pathology ordinarily is due to a tumor growth which destroys or causes pressure atrophy of the gland These tumors most commonly are craniopharyngiomas[19, 5, 8] Teratomas[97, 198] and cholesteatomas are relatively rare[194, 107, 188, 69] Those instances in which trauma to the skull has been associated with the onset of the arrested growth also have presented evidence of adenohypophysial tumors[9, 91] In some instances the pathology has consisted of extensive atrophy of the adenohypophysis presumably induced by embolism Hutchinson reported an atrophied hypophysis in a dwarf without noting any contributory factors[141, 142] Atrophy in other instances has been caused by inflammatory processes such as tuberculosis or syphilis[165] Tuberculous destruction of the hypophysis has been reported by Hueter[93] The writer has observed infantilistic dwarfism in an instance of Schuller Christian s disease where the xanthoma invaded the sella turcica and destroyed the hypophysis (Fig 32)

The degree of human dwarfism apparently depends on the age at which the pathological process develops and the length of time that it operates It is said that the degree of dwarfism may be related also to the extent of the damage to the adenohypophysis but there is no recorded evidence on this point Actually this may not be a reasonable assumption inasmuch as even minute remnants of normal adenohypophysial tissue appear to be able to maintain the metabolic functions of the gland to a remarkable degree Possibly other endocrine or perhaps hypothalamic factors are involved in this matter as suggested by the autopsy on Berblinger s[7] dwarf referred to later on in this section

As in the case of giantism the hypophysis was suspected of implication in dwarfism long before its growth regulating function was demonstrated Surprisingly few cases of so called hypophysial dwarfism and infantilism however have been studied thoroughly clinically and at autopsy

The first recorded instance of what has since been recognized as hypophysial



Fig 32 Schuller Christian s syndrome in a 19 year old boy Note dwarfism and genital hypoplasia with disproportionate skeletal measurements typical of eunuchoidism Autopsy disclosed complete destruction of the hypophysis cerebri Reproduced through the courtesy of the Department of Medicine Peter Bent Brigham Hospital.

dwarfism coupled with infantilism appeared in 1868[03] Schaaffhausen s patient was a male of average intelligence, 61 years of age and 94 cm in height There were three other examples of a similar condition among his brothers and sisters The conformation of the face and cranium were childish, the testes were un descended bilaterally and the epiphyses were ununited The post mortem examination following a terminal cerebrovascular accident was incomplete but the clinical picture is almost certainly that of adenohypophysial infantilistic dwarf ism In 1891 Paltauf[1 4] described a similar dwarf with infantile proportions ununited epiphyses and a markedly enlarged sella turcica In 1900 Hutchinson[14] called attention to a profound atrophy of the hypophysis in a dwarfed individual Levi s case[169] described in 1908 was a typical example of infantilistic dwarfism in which optic atrophy and x ray evidence of an hypophysial neoplasm were demonstrated The relatively frequent association of dwarfism and craniopharyn geal tumors was noted by Erdheim in 1916[04] Several carefully studied cases of dwarfism were reported by Erdheim[198] Altmann[193] Priesel[2 5] Berblinger[1 6 9] and Cushing[6] Erdheim s case, a male of 38 142 cm in height had infantile genital organs testes, penis seminal vesicles and prostate absence of facial, pubic and axillary hair and ununited epiphyses Autopsy disclosed a benign cystic craniopharyngioma which had become calcified and partially ossified Only traces of the adenohypophysis remained In Altmann s case a female of 17 129 cm in height the epiphyses were ununited A craniopharyngioma with ex treme atrophy of the adenohypophysis was found at autopsy Priesel described the case of a male 132 cm in height who showed beginning evidence of inhibited growth at the age of 15 but lived to the age of 91 His dwarfism was of the pro portionate type he was of good intelligence the epiphyses all became united but his testes remained small At autopsy the neurohypophysis was found behind the optic chiasm and the infundibulum it had never come into contact with the adeno hypophysis The latter was atrophic or rudimentary having been replaced almost entirely by a cyst that communicated with a widened portion of a persistent cranio pharyngeal duct

Berblinger s dwarf 144 cm in height was a male who died at 22 At the age of 15 he was only 135 cm in height and grew only 9 cm between then and the time of his death He had all the physical characteristics of hypophysial dwarfism and showed signs of intracranial neoplasm including headaches vomit ing attacks of vertigo diplopia left abducens paralysis and bilateral choked discs His intelligence was good X ray examination of the skull showed an enlarged sella turcica above which were some shadows due to calcification He died of pulmonary and intestinal tuberculosis and at autopsy the region of the infun dibulum was found replaced by an extra sellar partly cystic craniopharyngioma The pars tuberalis of the adenohypophysis and a portion of the floor of the third

ventricle were destroyed by the neoplasm which also displaced the floor of the third ventricle upward The bulk of the adenohypophysis was flattened by pressure, and on histological examination it was found that the chromophobe cells outnumbered the chromophile cells Berblinger believed that the injury to the adenohypophysis was not sufficient to render it non functional and concluded that the dwarfism was due to interruption of the connection between the adenohypophysis and the hypothalamus, possibly by way of the pars tuberalis

Pathological Physiology

Presumably the specifically damaged elements in the adenohypophysis are the acidophile cells which secrete the hormone regulating growth A detailed account of the biochemical and physiological significance of this hormone has been recorded in Part II of this chapter In this connection it is pertinent to recall the remarkable strain of congenitally dwarfed mice, the hypophyses of which are completely lacking in acidophile cells [07, 08] This strain of black silver mouse was brought to this country by Professor L C Dunn and described by Snell [09] who found that the dwarfism is not manifest until the end of the second week of life, when the natural process of weaning normally begins Development and growth practically cease at this time and the mouse is left in an infantile condition Smith and MacDowell [07, 08] reported a complete absence of acidophiles in the adenohypophysis Unfortunately their staining technic did not reveal whether or not basophiles were present The chromophobes were found to be much reduced in number if present at all The thyroids were much below normal in weight, and their parenchymal tissue was extremely reduced in amount and separated by unusual amounts of adipose and connective tissue Some of the thyroid tissue was not organized into follicles and contained little or no colloid The vesicles which were present were lined with squamous epithelium with flattened nuclei instead of the cuboidal type ordinarily seen in normal controls The adrenal cortex was found reduced in thickness, and the characteristic zonation was absent or indistinct The medullary cells appeared to be normal and contained the usual proportion of cells showing the chromaffin reaction The gonads although markedly retarded in development did not show as profound an aplasia as might have been expected from studies of hypophysectomized rats Development of the testes and other parts of the male reproductive system appeared only to be delayed Spermatocytes were present and undergoing division in the seminiferous tubules, and in occasional tubules there were fairly numerous spermatids The testes were not of the flabby variety characteristic of hypophysectomized rats

Development of the ovary was found to be further along than that ever seen after hypophysectomy although no medium sized or large follicles or corpora

lutea were encountered The ovaries became filled with interstitial tissue Subsequent biological studies [8] disclosed that there was a greater concentration of gonad stimulating hormone in the hypophyses of the dwarfed animals than in the glands of normal, mature female mice No significant amount of growth promoting substance could be demonstrated in the hypophyses of the dwarfed mice

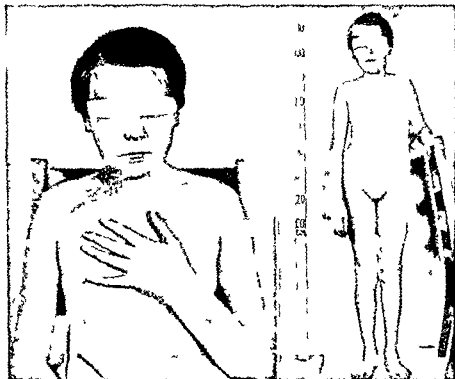


Fig 33 Hypophysial dwarfism in a 21 year old girl with chromophobe adenoma of the adenohypophysis Note childish appearance and genital hypoplasia Reproduced through the courtesy of the Department of Surgery Peter Bent Brigham Hospital

Judging from the condition of the gonads one might assume that basophiles were present in the hypophysis and functioning perhaps at a reduced rate because of the absence of the synergistic influence of the acidophiles The cytophysiological significance of these studies would be greatly enhanced were the condition of the basophiles known At any rate the absence of acidophiles seems to account quite satisfactorily for the dwarfed condition of the mice and possibly for the underdeveloped state of the thyroid gland

It is tempting to consider the possibility that these congenitally dwarfed mice, whose hypophyses are lacking in acidophile cells, are akin to the primordial variety of human dwarfism Further comment on this point is superfluous in the absence of autopsy material which has been studied adequately



FIG 34 Three primordial dwarfs siblings Male aged 30 years height in shoes 43 2 inches females aged 26 and 14 years respectively heights 37 2 inches and 34 4 inches respectively After Rischbieth and Barrington

General Appearance

Hypophysial dwarfs ordinarily are of good intelligence The syndrome is characterized by a proportionate diminution in size of the trunk extremities and internal organs The hands and feet are small and delicate The infantile size and proportions of the body and limbs are retained The limbs usually are particularly short, and the proximal segment humerus or femur may be shorter than

the distal portion Owing to the shortness of the lower limbs the middle point of the body is closer to the umbilicus as in infancy instead of being at the symphysis pubis as in normal adults The features of dwarfs are fairly stereotyped The hypophysial dwarfs particularly those with infantilism have the immature



FIG 35 Primordial dwarf Mlle Anita Age 23 years height 25 inches After Rischbieth and Barrington

appearance of children (Fig 33) The head is small and the configuration and measurements of the skull are those of the child The so called sexual ateleiotic (Gilford) or primordial (von Hansemann) dwarfs whose pathology is as yet unknown also have distinctive features which differentiate them from the infantilistic hypophysial dwarfs The face of the primordial dwarf is broad and flat the head is relatively large the bridge of the nose is undeveloped the nose is small and uptilted and the upper jaw is relatively short In typical cases although it is not universally so the facial type is so well defined that individualistic expression of character and personality is somewhat obliterated (Figs 34 and 35) This circumstance results in a strong resemblance between dwarfs of different families

As the childish features of the hypophysial dwarfs become lined with the superficial markings of age the facial appearance acquires an incongruously wizened

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the eighteenth century as was Charles Stratton in the nineteenth was Joseph Boruwlaski[1, 8] His parents who were of medium size had 6 children 3 of whom males are said to have exceeded the ordinary stature while 2 sons and one daughter did not attain a 4 year old height although they reached adult age Boruwlaski matured sexually at about the age of 25 became married at 40 and subsequently begot several children

Laboratory and Roentgen Data

In addition to the general appearance and lack of sexual development the significant clinical findings in hypophysial dwarfism include a low fasting blood sugar increased sugar tolerance abnormal sensitivity to insulin a moderately decreased or normal basal metabolic rate and x ray changes in the skeleton A basal oxygen consumption of −15 to −25 per cent is not unusual Whether or not these measurements are acceptable is questionable inasmuch as adequate standards are not available for these abnormal individuals

If these metabolic results are essentially correct one could attribute them to a lack of the direct calorigenic action of the adenohypophysis in addition to a failure in the production of thyrotropic hormone with secondary hypothyroidism The urinary excretion of neutral 17 ketosteroids and gonadotropin either is diminished markedly or absent entirely in accordance with the reported data of Klinefelter Albright and Griswold[6] and the experience of the author

X ray examination of the skeleton shows that the long bones are small slender and fragile The development of the carpal and metacarpal centers of ossifications may be normal but ordinarily they are somewhat delayed and occasionally markedly behind schedule[16, 3] The epiphyses remain ununited except in those rare hypophysial dwarfs who mature sexually or in the sexually mature primordial group of dwarfs[165, 7]

Roentgenograms of the skull of the hypophysial dwarf disclose pathognomonic evidence of adenohypophysial somatotropic insufficiency according to Mortimer Levene and Rowe Mortimer[10] and Goldzieher The face is small in relation to the cranium which thus remains largely infantile in type The brow retains the verticality of infancy The middle table of the thin and poorly differentiated calvarium is hypoplastic and can be made out only with difficulty The frontal sinuses are poorly developed and as a rule have not grown above the nasion The body of the sphenoid usually remains cancellous bone the sella turcica is infantile and the antra poorly developed The alveolar processes are hypoplastic and crowding of the teeth is marked Such crania closely parallel the results of hypophysectomy in the rat and dog[210]

expression To some extent this is due to the development of an atrophic wrinkled and pigmented skin The voice retains its childish treble pitch Dentition is very backward as a rule, to such an extent in some cases that many of the milk teeth are retained into the third and fourth decade of life The dwarfed jaws thus may become crowded with half erupted permanent teeth mingled with more or less decayed temporary teeth

Sexual Aspects

The lack of somatic development in hypophysial dwarfism is associated almost universally with retarded maturation and growth of the sexual apparatus On the other hand one may encounter instances of hypophysial deficiency, in which there is a specific lack in the production of either the growth or the gonadotropic hormones In such cases the resultant clinical syndrome is characterized by dwarfism without infantilism or gonadal hypoplasia without dwarfism respectively In patients of the latter category the skeletal measurements generally are those of the eunuchoid individual, and the total height is either ' normal " or somewhat in excess of this average figure The majority of hypophysial dwarfs remain sexually infantilistic Others, who mature sexually, are encountered only relatively infrequently

The genital organs of the infantilistic dwarfs of both sexes are markedly underdeveloped In the female there is hypoplasia of the ovaries tubes, uterus, vagina and labia majora and minora The labial, pubic and axillary hair is absent *as a rule, because of the adrenocortical atrophy, which occurs secondary* to adenohypophysial deficiency In the male there is retardation in the growth and development of the penis scrotum, testes and prostate, and the testes not infrequently are bilaterally cryptorchid The growth of pubic and axillary hair is lacking as in the case of the female hypophysial dwarfs Normal growth of the external genitalia spermatozoal maturation and the development of secondary sexual characteristics occur occasionally in dwarfed individuals, who seem to show little beyond the effects of a deficiency of the growth regulating hormone The epiphyses unite at the time of sexual maturity in dwarfs of the latter type but they remain ununited indefinitely in the infantilistic group Sexual maturity occurs much more commonly in the congenital primordial variety of dwarfism than in individuals who are stunted in growth because of functional insufficiency of the adenohypophysis

Tom Thumb the famous dwarf and Charles Stratton and his equally dwarfed wife are examples of the primordial type of dwarfism Mrs Stratton gave birth to an ordinary sized female child who died of an intercurrent infection during its first year of life[173] Another dwarf of the same type, quite as celebrated in

adrenal glands which were noted at autopsy by Gilford[1, 3] and by Variot and Pironneau[11]

Differential Diagnosis

Dwarfism due to adenohypophysial insufficiency must be differentiated from those cases of completely arrested or significantly inhibited somatic development, which are associated with agenesis and arrested development of the ovaries or secondary to nutritional deficiencies thyroid deficiency achondroplasia rickets and heart disease acquired congenitally or in infancy

The combined observations of a number of investigators[187 1 1 8 190 191 18] have disclosed several distinctly helpful criteria which serve to differentiate the stunted somatic growth associated with primary ovarian deficiency from dwarfism due to adenohypophysial pathology In general patients with primary ovarian insufficiency are relatively short rather than dwarfed in stature, and they appear to be well developed and nourished rather than frail and underweight as is the case in hypophysial dwarfism Both conditions are characterized by sexual infantilism with complete absence of the so called secondary sex characteristics but there is a limited to moderate growth of axillary and pubic hair in the syndrome of ovarian deficiency, whereas none at all grows in the hypophysial dwarf The latter has been attributed to atrophy of the adrenal cortex secondary to adenohypophysial deficiency[18 190 19] The bone age of hypophysial dwarfs may be considerably retarded while that of patients with primary ovarian insufficiency is retarded only slightly if at all Certain laboratory studies have been especially useful in this differential diagnosis The hypophysial dwarfs show increased sugar tolerance marked sensitivity to insulin and markedly diminished or absent excretion of urinary gonadotropin and neutral 17 ketosteroids In the case of primary ovarian insufficiency there is no significant deviation from the normal average response to the administration of glucose or insulin the urinary content of FSH is markedly elevated as a rule and the 17 ketosteroid excretion is only slightly decreased The excretion of urinary gonadotropin is not elevated invariably to a marked degree in patients with primary ovarian deficiency The reason for this unexpected discrepancy is not apparent unless one assumes that the gonadotropic activity of the adenohypophysis is damaged selectively coincidentally with the agenesis or arrested development of the ovaries in such cases

The differentiation of hypophysial dwarfism from hypothyroid nanosomia is a relatively simple matter even though a number of important abnormalities of development are common to both of them The essential characteristics of the hypothyroid dwarf vary with the age of the patient as one might expect from a disorder which cripples the various integrated phases of somatic sexual and mental development For the present purpose it is sufficient to point out that before the

Clinical Course

The growth behavior of hypophysial dwarfs lacks uniformity The disorder may appear at any age beginning shortly after birth Many of the dwarfs cease to grow entirely in childhood or youth some continue to grow at a slow pace into the third or fourth decades as long as the epiphyses remain ununited while occasionally growth ceases only for a time after which it is renewed to a limited extent The latter also may be characteristic of the primordial dwarfs and occurred in the case of the celebrated Jeffrey Hudson, who remained 18 inches tall from 8 to 30 years of age, after which he grew to 3 feet, 9 inches[1,3]

The hypophysial dwarf in contrast to the giant has a relatively long life expectancy unless there is excessive enlargement or malignancy of the hypophysial tumor or unless progeria develops Since most of these tumors are benign, they are not actively detrimental to life

Hypophysial dwarfism has been noted in association with adiposogenital dystrophy and diabetes insipidus[1] , ordinarily, however, these dwarfs are not obese

Progeria —Progeria is a rare complication of hypophysial dwarfism which develops at a relatively early age and is progressive It is characterized clinically by cachexia premature senility and infantilistic dwarfism Hutchinson s patient[1,3] who showed signs of this condition at 3½ years of age died at 14 The skin is thin, dry and old looking Axillary pubic and facial hair are absent, a sparse growth of hair may be present on the scalp eyebrows and eyelids The extraordinary emaciation reveals even the nasal cartilages The muscles are poorly developed and weak Gilford s patient[173] who died at 18, had ununited anterior fontanelles at 14 years of age when he was last studied His dentition was delayed and crowded his voice was pitched high and his sexual development seriously impaired He died a cardiac death At autopsy there was extreme emaciation a persistent enlarged and fibrous thymus and extensive atheroma of the mitral and aortic valves the coronaries were solid thick cords and completely blocked the kidneys were fibrous senile the suprarenal capsules were shrivelled, the stomach and intestines were extremely atrophied the liver relatively large, the long bones small and delicately formed with ossification generally a little premature The brain was said to be normal and examination of the hypophysis was passed over casually because it seemed unimportant A third case has been reported by Variot and Pironneau[11]

Progeria appears to be the juvenile form of Simmonds cachexia in combination with hypophysial dwarfism but positive proof of this clinical impression is not yet available This assumption would account adequately for the atrophic

spread belief these developmental anomalies are by no means pathognomonic of juvenile myxedema nor can they be used to differentiate this condition from hypophysial dwarfism The extent of the delay in these processes of bone development and growth *usually is less in hypophysial dwarfism than in hypothyroidism* but the fact that the difference is quantitative not qualitative obviates its usefulness as a differential diagnostic point As a matter of fact there are individual examples of hypophysial dwarfs in whom these defects are as striking as in the nanosomia of hypothyroid origin

In infantile myxedema the circumference of the skull does not correspond to *the age of the individual but is distinctly larger in proportion to the rest of the* skeleton This is true also of another type of dwarfism viz that described by von Hansemann as primordial nanosomia and by Gilford as sexual ateleiosis It is this writer s impression however that the infantilistic dwarf of Paltauf s type which is identical with asexual ateleiosis of Gilford von Hansemann s infantile dwarf whether of hypophysial origin or secondary to nutritional deficiencies etc *is more likely to have a skull relatively small for his age but which is in proportion* to the size of the rest of the skeleton

So far as the bones are concerned the only differential point between hypophysial and hypothyroid dwarfism lies in the x ray appearance of the shaft of the long bones In the former the bones are slender and fragile in appearance and the cortex is thin in the latter the bones are relatively heavy and thick and *show a slight degree of sclerosis Breus and Kolisko and Bircher*[2 3] have observed an additional differential point between endemic cretinism and the Paltauf type of dwarfism viz that the endemic cretin has a disproportioned skeleton because epiphyseal union takes place at a different rate and to a different degree in various bones whereas all epiphyseal closures are delayed equally in hypophysial dwarfism

The hematopoietic system suffers seriously in hypothyroidism the *hemoglobin* is reduced relatively more than the erythrocytes In hypophysial dwarfism the total erythrocyte count ordinarily is within normal limits but the hemoglobin may be somewhat reduced In both conditions there is a well marked relative lymphocytosis and eosinophilia

The rachitic and achondroplasic dwarfs offer no problem in differential diagnosis X ray studies of the ends of the long bones and the classical bony deformities of the rachitic individual i e skull changes pigeon breast Harrison s groove rosary bow legs etc leave little doubt as to the etiology of this type of somatic maldevelopment The achondroplasic dwarf is recognized readily by the disproportionate growth of trunk and extremities Such persons have a full sized head and trunk associated with incongruously short extremities Not only are the long bones of the arms and legs abbreviated but the base of the cranium is dis-

fourth and fifth year the hypothyroid dwarfs do not exhibit the coarse, dry, thick integument usually associated with juvenile myxedema Although the skin of the infant hypothyroid is thicker than normal, it remains quite smooth, and there are subcutaneous fatty pads at the nape of the neck and in the supraclavicular regions These fatty pads are absent, and the skin is thin and soft in the hypophysial variety of dwarfism The face of the hypothyroid individual derives its characteristic cretinoid appearance from the position of the horizontally placed, slit like eyes and from the depression at the root of the nose, which is due to a delay in development of the nuclei of ossification of the vomer In addition there is a vacuous facial expression and behavioral evidence of retarded mental development The hypophysial dwarf on the other hand, retains a childish facial expression and may be retarded psychologically but not mentally Di Gaspero [1] attaches a special significance to the retention of childish ideas of values and logic He finds in the infantilistic dwarf a childish instinct for mimicry and a certain attitude of anxiety and non independence Anton [13, 14], who is in general accord with Di Gaspero has observed also that these individuals usually lack the childish tendency toward gaiety and freedom

In both of these types of dwarfism there is delayed and abnormal dentition The milk teeth develop very slowly and finally remain partially retained Rudiments of the permanent teeth become mixed with the milk teeth Failure to walk and talk at the usual age the enlarged thick protruding tongue the hoarse cry, the umbilical hernia the protuberant pot belly and chronic constipation are additional clinical features limited to juvenile myxedema A serious retardation in genital development is common to both forms of dwarfism In the female there is marked hypoplasia of the external and internal genital organs The labia majora are stunted and do not cover the labia minora the uterus is underdeveloped and the breasts fail to grow In the male the penis is small, and the testicles do not descend ordinarily If they do enter the scrotum, they usually remain infantile There is no change in voice unless sexual maturity takes place Pubic and axillary hair ordinarily is absent in both sexes

In general the dwarfed skeleton retains the child like body proportions in both disorders and a delay in closure of the fontanelles also is characteristic of both conditions Argutinsky [15] has observed that there is a greater delay in the development of the bone nuclei than in the linear growth of the long bones in sporadic cretinism Thus, if the height of a 20 year old cretin corresponds to that of a 6 year old normal child the appearance of the nuclei of ossification are even considerably further behind Delay in the closure of epiphyses and retardation in the time of appearance and development of the various centers of ossification are constant features of hypothyroid dwarfism[1, 13, 15, 16, 17, 18, 19, 20, 21], which can be determined conveniently by x ray examination of the wrist Contrary to wide

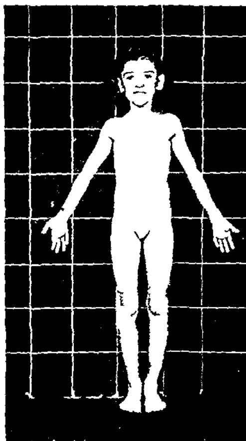


Fig 36 Infantilism and dwarfism History of severe qualitative and quantitative nutritional deficiencies Marked and immediate growth response to balanced diet supplementary vitamins and methyl testosterone Age 9½ years Reproduced through the courtesy of E Kost Shelton MD

"hypophysial dwarfs 3 of whom eventually turned out not to be of hypophysial origin [5] Another factor contributing to the difficulty of evaluating the efficacy of therapy or lack thereof is the inadequately controlled experimental conditions under which the therapeutic trials are made Many of the cases treated successfully are given physiological doses of thyroid simultaneously with an adenohypophysial growth promoting extract without first testing the patient s growth re

proportionately short so that the face is flattened and depressed at the nasion saddle shaped, and the forehead consequently is prominently rounded The epiphyseal cartilages in the extremities and the basicranial cartilage in the head are deficient with more or less connective tissue hyperplasia and fail to give the usual growth of the long bones In some of these dwarfs the coccygeal vertebrae are fused and bent in direction The extremities are short and considerably bowed and twisted As a rule the proximal segment of both extremities, humerus and femur, are more shortened than the distal segments The hands and feet may be simply stocky and wide in appearance The posture of the hands and feet tends to abduct or outspread the digits to varying degrees The arms and hands are moved in a characteristic manner The hand cannot be brought to the mouth without abducting and raising the elbow almost shoulder high This condition is caused by the spiral twist in the long bones, which affects the plane of flexion of the elbow joint The sexual development of the achondroplasic dwarf generally is quite normal and the epiphyses unite at the proper time Occasional instances of a slightly delayed closure of the epiphyses are encountered in individuals with a somewhat retarded sexual development

The obvious importance of nutritional factors to the normal progress of growth (Fig 36) makes it essential to investigate the patient s past history thoroughly for evidence of malnutrition either as the result of socio economic and environmental conditions or of gastrointestinal renal or cardiac disturbances The distinction between primary and hypophysial dwarfism or infantilism and retarded somatic and sexual development secondary to nutritional disorders is not a simple one to make In many instances the two groups of conditions overlap, especially when malnutrition has damaged the adenohypophysis secondarily The attempt at differential diagnosis is important however because of the necessity for specific therapy, viz a well balanced diet, supplementary vitamins, sunshine, etc

Treatment

There is every reason to believe that the adenohypophysial growth hormone has been used more widely in the treatment of hypophysial and other forms of dwarfism than the relatively few reports in the literature would indicate This probably signifies that many of the studies yielded negative results which investigators were loth to report Furthermore the results of the published investigations are variable and contradictory These inconsistencies may be attributed in part to certain difficulties in the diagnosis of hypophysial dwarfism Even in the hands of experienced investigators the nature of the fundamental disorder frequently is not established until the clinical course of the patient discloses it Such was the report of Shelton Cavanaugh and Evans[2 4], who studied a series of 6

under chorionic gonadotropin therapy an increase in the growth rate beyond the expected average has been observed by Lurie and Hertzman [1] Dorff [35] Thompson and Heckel [6] and Finkler, Furst and Cohn The range of dosage used to accomplish these results has been fairly wide averaging from a total of 9 000 to 40 000 rat units which are equivalent to international units Treatment usually has been administered in doses of 250 to 500 i u per week over a period of 4 to 8 weeks with intervals of 4 to 6 weeks between each series of injections

As in the case of chorionic gonadotropin various compounds of testosterone have been administered to somatically and sexually underdeveloped boys principally for the treatment of their gonadal and genital hypoplasia Various recognizable endocrinopathies characterized by these deficiencies have been treated successfully with testosterone [0 1 1 3] Most investigators have resorted to a descriptive terminology rather than one aimed at stating the primary nature of the growth disorder For instance Finkler Furst and Cohn include many instances of cryptorchidism and growth retardation among their patients but without any attempt at further diagnosis It is this writer s experience that testosterone propionate or methyl testosterone are effective in the treatment of hypophysial dwarfism associated with sexual infantilism [8]

There is good experimental evidence which relates the efficacy of testosterone to growth Castration of male rats in early life results in significant inhibition of general somatic development and retardation in body length as compared to normal controls Rubenstein and Solomon [9] have reported an increase in the body length of white rats following the administration of small doses of various testosterone esters whereas large doses exert a depressing effect which exceeds that of castration alone Turner and associates [41] also found that large doses of testosterone propionate given over prolonged periods of time did not accelerate body growth or skeletal maturation in rats except in isolated instances

A good deal of controversy has centered about the possible deleterious effects of testosterone therapy viz the hazards of testicular damage, premature closure of the epiphyses and macrogenitalia Until relatively recently it was believed because of limited physiological experiments that the administration of testosterone always induced atrophy of the testes although it stimulated the growth of the penis scrotum seminal vesicles and prostate as well as development of pubic and axillary hair Rubenstein and Kurland [4] state however that small doses of testosterone propionate (5γ) injected daily into male rats from 22 to 32 days of age results in a significant increase in the weight of the testes and stimulation of proliferation of the germinal epithelium but maturation of the spermatozoa remained unaffected With much higher doses (50γ) the testicular weight diminished but all testes showed signs of increased germinal proliferation Intermediate doses affected the testes adversely in every respect Shay and asso

sponse to thyroid alone[6] Although the thyroid hormone may enhance the growth promoting qualities of an adenohypophysial extract and from this point of view seem indicated there is no way of knowing what thyroid alone might have done Even when adequate clinical controls are set up, an untreated hypophysial dwarf suddenly starts growing to the extent of 6 inches (15 2 cm) in 22 months *It is doubtful* moreover, *whether the earliest reported successes can be accepted* as such, because of the relatively low growth promoting potency of the extracts then in use

A survey of the literature and the writer s own experience with the therapeutic efficacy of adenohypophysial growth promoting extracts in hypophysial dwarfism indicate that isolated cases seem to have responded significantly but the results in general leave much to be desired The latter is decidedly not applicable to *the growth stimulating effects which have been observed after the use of chorionic* gonadotropin or testosterone propionate or a combination of the two

The value of chorionic gonadotropin as a therapeutic agent in dwarfism was recognized as a result of its use for the correction of genital and gonadal hypo plasia Following the discovery of this gonad stimulating substance in pregnancy urine by Aschheim and Zondek[27], Engle demonstrated [8] that an increase in the rate of growth of the sex organs of the immature rat could be produced by its injection Schapiro [9] *subsequently applied this knowledge clinically to cases of* genital hypoplasia and cryptorchidism The use of chorionic gonadotropin be came more extensive following Engle s demonstration [?] that testicular descent was induced in monkeys with delayed puberty by injecting extracts of pregnancy urine

Since then there has been accumulated an extensive literature dealing with this type of endocrine therapy for cryptorchidism This has been reviewed by Bigler Hardy and Scott[31] Nixon and Finkler, Furst and Cohn[9] among others Unfortunately in most of the reported cases the clinical emphasis has been on the condition of the genitalia and little or no attempt was made to differentiate one type of growth retardation from another The treated patients showed almost invariably a combination of various degrees of dwarfism genital hypoplasia and gonadal underdevelopment including cryptorchidism So far as one can judge instances of hypophysial dwarfism are to be found among these successfully treated examples of sexual and somatic infantilism

A wide divergence of opinion is to be found among investigators concerning the efficacy of this form of therapy for cryptorchidism Reports of successful re sults range from 20 to 70 per cent More extensive experience in the selection of patients has disclosed that true cryptorchidism has yielded to this form of therapy in an average of about 30 to 40 per cent of the cases [1 3 33 234]

Coincident with the improvement in the genital development of these boys

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ciates [13] found similarly that large doses resulted in an increase of testis weight and stimulation of spermatogenesis They concluded that the immature germinal epithelium can be stimulated to increased activity but not to earlier maturation It is still too early to discuss this problem as it applies to human beings with any degree of assurance but in this writer s experience no harm has been done with moderate dosage [3] It is certainly clear that moderate amounts of the testosterone esters do not produce untoward epiphyseal development or premature closure of the epiphyses[16 34 44 4 40 4 48]

Ordinarily a favorable response in linear growth and sexual development is elicited following the administration of 10 mgm testosterone propionate parenterally 3 times a week or 10 to 20 mgm methyl testosterone orally 4 to 7 times per week The dose has to be adjusted in each case so that neither frequent priapism nor too rapid growth of the penis occurs

Dwarfism also is discussed by Arthur Grollman in Vol III, Chapter XIX, of Oxford Medicine

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Cytology with Special Reference to Pituicytes

As compared with the adenohypophysis relatively little is known of the cytology of the neurohypophysis Data available at present indicate that there are several different varieties of cells in the lobus nervosus a subdivision of the neurohypophysis which has been studied more particularly than the infundibular stem or the median eminence of the tuber cinereum The cells which have been described include the neuroglia like pituicytes isolated nests of large pale cells and invading basophile cells which take origin from the pars intermedia Undoubtedly there are other parenchymal cells which remain to be recognized and described judging from the complex cytological appearance of this portion of the gland In this connection it is well to recall that apparent cytological differences between cells of the same general type may represent various metabolic phases of cellular activity rather than functionally different parenchymal cells An excellent example of this general rule was encountered by Gersh in the pituicytes of the rat s neurohypophysis which changed remarkably with hydration and dehydration of the animal

The pituicytes so named by Bucy are to be found in all divisions of the neurohypophysis The topographical distribution of these cells is coextensive with the sites from which the antidiuretic principle has been extracted Moreover the pituicytes have been identified in all orders of mammalia whose glands have yielded this hormone It is interesting furthermore that the distribution of these cells is that which might be expected from the most recent conception of the pathogenesis of diabetes insipidus In appearance the pituicytes are fusiform and irregularly shaped cells provided with delicate branching processes Geiling and Robbins[11] report that in the white whale these cells have stout processes which end with expansions on the connective tissue of the capsule or of the walls of the abundant blood vessels Geiling[1] likens their structure to ependymal spongioblasts of the embryonic central nervous system or to the cells of ependymal tumors

Some of the pituicytes are definitely granular while others are devoid of granules probably depending on the phase of their functional activity Although superficially similar to the neuroglia of the central nervous system they are distinctive cytologically from these and all other cells of the hypophysis cerebri In the various orders of mammalia studied by Gersh[10] there is clear-cut differentiation of pituicytes from other cells of the hypothalamo hypophysial area In the neurohypophysis of the rat and mouse these parenchymatous cells contain cytoplasmic inclusions rich in neutral unsaturated fats which are stained by Sudan III and reduce osmic acid readily In ox glands the histochemical reactions of the intracellular inclusions indicate that they are protein in nature The cytoplasmic

Part V

CYTOPHYSIOLOGY, BIOCHEMISTRY AND PHARMACOLOGY OF THE NEUROHYPOPHYSIS

Histology and Cytology of the Neurohypophysis

General Histological Characteristics

It was indicated in the opening paragraphs of Part I that the neurohypophysis consists of a functional unit which is made up of the median eminence of the tuber cinereum, the infundibular bulb the infundibular stem and the infundibular process In general these neural subdivisions of the hypophysis cerebri contain the following histological elements (a) a meshwork of connective tissue fibrils, which are composed largely of reticulin with some collagen according to Bucy[1] (b) a capillary plexus the origin and distribution of which has been described under an appropriate heading elsewhere in this chapter (c) unmyelinated nerve fibers which enter the neurohypophysis via the median eminence and infundibular stem in the form of the supraoptico hypophysial the paraventriculo hypophysial and the tubero hypophysial tracts These tracts give off innervating fibers to the various parts of the neurohypophysis through which they course, and finally spread out into a dense meshwork in the infundibular process Here they come into pericellular relations with the pituicytes which will be described later It has been established with some certainty that the paraventricular nucleus sends only a few fibers into the processus infundibuli and that most of its fibers end in the region of the supraoptic nucleus and the median eminence of the tuber cinereum[2] The supraoptic nucleus is thought to be the origin of nearly all of the fibers entering the processus infundibuli and the so called tubero hypophysial tract may arise from the attenuated posterior end of the supraoptic nucleus according to Rasmussen[3] (d) relatively few unmyelinated nerves which are the post ganglionic fibers of the superior cervical sympathetic ganglia and enter the neurohypophysis with its vascular supply (e) various types of cells including the specialized glial cells known as pituicytes large pale cells of unknown origin and function[4, 6, 8], basophile cells which arise from the pars intermedia and invade the processus infundibuli wandering cells[1] and mast cells[9]

connected with the hypophysial cleft by ducts through which a seroalbuminous secretion is poured into the cleft Bucy believes there can be little doubt from the histological appearance that they are true glands In accord with Erdheim[16] and Lewis and Lee[17] Bucy regards them as derivatives of the buccal mucosa and thus relates them to the salivary glands Histogenetic studies indicate that they belong to the pars intermedia Microscopically the glands are composed of numerous branching acini uniting at a common duct They are lined by a single layer of pyramidal cells with a pale spherical nucleus near the base The apices of the cells contain a highly refractile colloid like substance whereas the cytoplasm is finely granular in general The duct of the gland is formed by a low cuboidal epithelium quite unlike that of the acini

Beyond four years of age the number of these glands decreases and certain of them become distended with their own secretions forming small colloid cysts which are encountered near the junction of the adenohypophysial and neurohypophysial tissues in the zone of the pars intermedia These cysts are lined by a flattened cuboidal epithelium among the cells of which a few basophilic cells can be seen frequently The basophiles are relatively large with a round or ovoid shape and their cytoplasm is filled with many basophilic granules In adults masses of basophilic cells appear in the lobus nervosus[7 8 18 19] in addition to colloid cysts Apparently the basophilic cells develop at least in part from the glandular structures

Guizzetti[4 15] has observed narrow cords of cells arising from the pars intermedia and extending into the pars nervosa in the first year of life About the seventh year these cells become transformed into basophiles This invasion and transformation is not a constant finding Guizzetti observed it in one third of the cases between 10 and 20 years two thirds between 20 and 30 and four fifths between 30 and 85 years Sparks Rasmussen[19] and others before them have called attention to the fact that the basophilic cell invasion is greater in the hypophyses of males than of females Careful statistical studies have failed to correlate the extent of invasion with various clinical disorders characterized by hypertension[7 8] [1] The most extensive invasion is said to take place from that part of the pars intermedia which is in contact with the inferior portion of the lobus nervosus [14 15] Where the basophilic invasion is limited to one area it is also more likely to extend into this p rt of the neurohypophysis

The Hyaline Bodies of Herring

Herring was among the earliest to call attention to the loose mesh like appearance of the tissue of the neurohypophysis He observed that interstitial spaces lined with endothelium in some instances contained peculiar homogenous

granules are very nearly uniform in size in any particular cell but may vary considerably in different cells according to Gersh[10]. Serial sections of the pituicytes disclose that the granules extend far out into the cell processes. These are the cells undoubtedly in which Bucy[1] observed granules of brown pigment, which stained readily with neutral red. The amount of the pigment appears to increase gradually with age.[8] Kraus has made similar observations, but since the hypophyses from elderly individuals occasionally show little or no pigment, he believes that there is no significant relation between age and this type of pigment. Presumably this pigment is identical with the cytoplasmic inclusions which have been described by Gersh[10].

The isolated nests of large pale cells, which occur in the processus infundibuli, probably are of physiological significance but the latter has not been determined as yet. They have been described by Kraus, who quotes several authors concerning them: by Simonds[4] who describes them in two cases, by Sparks, who pictured them in one case, by Sternberg and Priesel[6], who found that they measured 30 to 50 micra in diameter and by Parsons[8], who observed them in 13 of 107 glands which he studied.

These nests of cells vary in size from those containing only a few cells to groups of cells which measure 0.5 mm in diameter. The nests usually are single, and Parsons states that ordinarily they are found to one side of the median line in the posterior half of the lobus nervosus. These cells have a distinct cell boundary, which stains more intensely with aniline blue than other parts of the cell. The cytoplasm is abundant and loosely packed with granules which take the acid dye when stained with hematoxylin and eosin. The nucleus is large and vesicular and is located eccentrically. The nests lie in the interstices of the tissues of the lobus nervosus.

Small capillaries and light strands of connective tissue penetrate between these cells whose function and origin still remain to be determined. Kraus[5] has suggested that they represent cell nests of ependymal origin. They may be derived from the saccus vasculosus to which reference was made in Part I of this chapter. Parsons has observed single cells similar to but smaller than those just described which occur in the interstices of the lobus nervosus. They have a normal nucleus and a distinct cell membrane which distinguishes them from the structures that Cushing[1, 13] thought were derived from the basophilic cells in the lobus nervosus.

Numerous careful observations which have been made of the epithelial cells in the lobus nervosus indicate that their cytological characteristics and distribution change with advancing age but the physiological significance of these alterations is wholly obscure. Tubulo racemose glands are a feature of the neurohypophysis during the first four years of life according to Guizzetti[14, 15]. They are

PHARMACOLOGY AND METHODS OF ASSAY OF THE NEUROHYPOPHYSIAL PRINCIPLES

General Considerations

Only three of the numerous biological activities which have been attributed to neurohypophysial extracts are sufficiently well characterized to merit identification as pharmacological properties of the neurohypophysis itself These are the effect upon mammalian blood pressure upon uterine muscle and upon the rate of excretion of urine viz the pressor oxytocic and antidiuretic activities respectively

Other effects that have been observed may be due to substances which arise in portions of the hypophysis other than the lobus nervosus or they may have been elicited by substances like histamine which are extractable from a variety of animal tissues

The Pressor Effect

The bioassay method for the pressor principle has been developed largely through the studies of Hamilton and Rowe [34 35]

The solution to be assayed is injected into the leg vein of an anesthetized cat or dog and it is followed by an injection of the reference standard after an interval of 15 minutes The pressor standard used is a powdered preparation of the desiccated lobus nervosus of fresh beef glands which contains 2 International Pressor Units per mgm when prepared as prescribed by the U S Pharmacopoeia This preparation has been adopted as the standard for pressor and antidiuretic assay [6] and it has been agreed further that 1 mgm of the standard powder contains 2 units of each of the three pharmacological activities of the neurohypophysis

The pressor assay dose varies between 0 1 and 0 5 units 0 05 to 0 25 mgm of the standard powder This dose usually induces an increase in blood pressure of about 10 mm of mercury The mercury manometer which registers these changes in blood pressure in a cannulated carotid artery transmits the impulse to the smoked drum of a kymograph Alternate injections of the unknown and the standard are made at 15 minute intervals until the increase in blood pressure due to varying amounts of the unknown is approximately equal to that produced by the standard in at least two successive paired experiments

Since the pressor content of the standard dose is known the ratio between the heights of the standard and unknown responses gives the pressor content of the unknown substance which has been injected The accuracy of this method is said to be ± 20 per cent

or granular clumps of material, which varied considerably with respect to size and shape These tissue spaces occurred between parenchymal cells, which are now known as pituicytes and extended throughout the neurohypophysis, including its infundibular stem and medium eminence Herring postulated that these hyaline bodies were the product of secretion of the pars intermedia, and that they ascended the infundibular stem to enter the cerebrospinal fluid through the wall of the third ventricle

Many investigators have been concerned with the origin, physiological significance and fate of the hyaline bodies since Herring s report Most authors have referred to them as colloid and thought that they represented the product of secretion of one or another of the various parts of the hypophysis cerebri Tello [3] and Bucy on the other hand regard the Herring bodies as degenerated end bulbs of the nerve fibers of the hypothalamo hypophysial tracts, which terminate among the pituicytes The most recent attempt to interpret the significance of the Herring bodies is that of Gersh [4], who came to the conclusion that they are histological artifacts which do not exist in the living animal His studies indicated that this material had the solubility properties of an albumen and occurred as a protein which was uniformly distributed in the intercellular tissue fluid of the neurohypophysis He postulated furthermore, that this substance represented plasma proteins, which had passed through the capillary wall because of its great permeability to particles of colloidal dimensions" On the basis of studies which were mentioned without details Gersh concluded that there was no identity between this uniformly distributed protein and the pressor principle One might raise a question concerning the propriety of using the term artifact, to characterize the Herring bodies It implies that they do not exist except as an accident of technic The fact that these so called bodies are altered in size, shape and distribution with variations in the rapidity of fixation should not affect their significance in the physiological scheme of things Evidence cited further on in this section indicates that the neurohypophysial principles are polypeptides with molecular weights between 600 and 2 000 [6 7 9 9 30] There is reason to believe, furthermore that a homogenous protein possessing the pharmacological activities of all three of the neurohypophysial hormones has been isolated from the lobus nervosus of oxen[21] and ultracentrifugal data support this evidence In view of these chemical and physical properties it seems desirable to reinvestigate the abundant protein material of the Herring bodies with the thought that they may represent histochemical evidence of the hormonal secretion of the pituicytes In this connection one might point out that the extent of distribution of this protein material is identical with that of the pituicytes which may be a more likely reason for its presence in the region of the tuber cinereum than the reason advanced by Herring[2]

several rats in doses of 5 c c per 100 gm body weight The solution to be assayed *is injected subcutaneously into each animal and the rats are caged together* The time is determined for the rate of urine excretion to reach a maximum or for the urine excretion to equal 50 per cent of the administered water This experiment is controlled by an equal number of rats treated similarly except that a known amount of a solution of the standard powder is injected instead of the unknown solution The dose of standard powder used for assay is approximately 0 006 units per 100 gm body weight Usually this amount reduces the rate of urine excretion to about 50 per cent of that found in the untreated hydrated animal The ratio between the standard and unknown time intervals serves as a basis for calculating the antidiuretic activity of the unknown This bioassay method is capable of differentiating doses differing by as little as 0 002 unit which is equivalent to about *one microgram of standard powder* The *experimental error is in* the vicinity of ± 20 per cent if the test animals are selected properly

Biochemistry of the Neurohypophysial Principles

Evidence Bearing on the Unitary and Multiple Concepts of Molecular Configuration

It is not known definitely whether one or more than one active principle exists in the lobus nervosus under physiological conditions Abel and his co workers[41] have suggested that the oxytocic antidiuretic and pressor activities were properties of a large labile mother molecule Evidence for this assumption was offered recently by Van Dyke Chow Greep and Rothen[3] who isolated from the lobus nervosus of oxen a protein which appears to be homogenous and which possesses pressor oxytocic and antidiuretic activities Furthermore studies with the ultra centrifuge have disclosed that the pressor and oxytocic activities in the pressed juice from fresh glands may be associated with a rapidly sedimenting substance *presumably a protein which is not present in purified preparations of the two* principles

Chemical and Physical Characteristics of the Pharmacologically Active Principles

None of the three neurohypophysial principles which have been enumerated has been prepared in pure crystalline form Fractionation procedures have yielded non crystalline amorphous preparations either of high pressor potency and very low oxytocic activity or high oxytocic potency and negligible pressor activity There is considerable additional evidence which indicates that the pressor and

The Oxytocic Effect

The official method of the U S Pharmacopoeia XII is a sensitive modification of the original uterine strip procedure[37, 38] This method makes use of healthy, virgin, non estrous guinea pigs weighing between 175 gm and 350 gm It is recommended that the young female guinea pigs be segregated at the time of weaning and kept thereafter out of the sight and smell of males

The guinea pig is prepared for experimentation by a blow on the head or by decapitation and the entire uterus is removed from the body immediately One horn of the uterus is suspended in a chamber containing oxygenated Locke Ringer s solution at a constant temperature of 37° C One end of the horn is fixed and the other, or free end is attached to a light muscle lever which registers the extent of movement on a kymograph drum The lever may be weighted, if necessary but the amount of this weight must not be changed while the contractions constituting the assay are being obtained When the uterus is completely relaxed which generally takes about 15 to 30 minutes, the assay may be started Suitable quantities of the standard solution and of the preparation to be assayed are diluted with an isotonic solution of sodium chloride The solution to be assayed and the standard solution, containing 2 oxytocic units per mgm of standard powder, are added to the bath alternately in varying doses until quantities of the two solutions are found which give equal submaximal contractions in at least two successive pairs of responses, i e a series of four contractions of approximately the same height The bath solution is discarded and replenished after each contraction A third dose of the standard solution, which is 25 per cent larger than the two preceding doses of the diluted standard solution then is administered The first four contractions constitute an assay, if the difference in height between the highest and lowest of these four is less than half the difference in height between the lowest of the four and the contraction resulting from the reference standard the dosage of which was increased by 25 per cent The oxytocic activity of the preparation to be assayed is calculated in terms of U S P Posterior Pituitary Units from the ratio between the unknown and standard responses

Owing to the many variable factors in the assay of the oxytocic principle, an accuracy of ± 20 per cent is acceptable

The Antidiuretic Effect

The bioassay method usually employed for the quantitative determination of the antidiuretic hormone is the Burn[39] modification of the Gibbs[40] technic Water is administered by stomach tube or intraperitoneal injection to each of

observations because a well defined connective tissue septum makes possible a complete separation of the lobus nervosus (infundibular process) from the adjoining lobus glandularis Furthermore there is no histological evidence of a pars intermedia in the chicken or the whale[1] It was possible thus to prepare extracts of the adenohypophysis and neurohypophysis free of each other and uncontaminated with pars intermedia Such extracts of the infundibular process contain a concentration of antidiuretic hormone which equals that extractable from the lobus nervosus of the ox gland[11] and this hormone is not to be found on assay of the adenohypophysial extract[1] *These conclusions have been confirmed* by histological and pharmacological studies in cats with experimental diabetes insipidus The infundibular process which is atrophic in such cats contains greatly reduced amounts of antidiuretic principle as compared with normal animals while the pars tuberalis and pars intermedia of the adenohypophysis were found to be anatomically and pharmacologically normal in operated animals with chronic polyuria [9] It appears to be functionally significant furthermore that *the pattern and permeabilities of the vascular bed of those portions of the neurohypophysis* in which the antidiuretic substance is elaborated have special characteristics which *differ from those observed in other parts of the hypophysis* and central nervous system The vascular pattern of the infundibular process extends over the infundibular stem into the median eminence where it is sharply demarcated from that of the hypothalamic circulatory system and the permeabilities of these capillaries differ from those of all other vessels in the other portions of the hypophysis and the remainder of the tuber cinereum[60, 16]

Secretion of the Antidiuretic Substance by the Pituicytes

Functional Innervation of the Pituicytes — *The* secretory cells of the median eminence of the tuber cinereum are connected with the paraventricular and supraoptic nuclei of the anterior hypothalamus by well defined neural pathways the paraventriculo hypophysial and supraoptico hypophysial tracts Another group of fibers constituting the tubero hypophysial tract is thought by some[53] to take origin in the nuclei of the tuber cinereum but Rasmussen states that it may arise from the attenuated posterior end of the supraoptic nucleus These nuclei of *the hypothalamus the neurohypophysis and the fiber tracts which connect them, represent a functional unit* *Pathological destruction or ablation of the neurohypophysis results in atrophy of the cells of the hypothalamic nuclei* and similar damage to the supraoptic nuclei is followed by atrophy of the neurohypophysis Transection or destruction of the supraoptico hypophysial tract results in cellular degeneration of the lobus nervosus and the hypothalamic nuclei and diabetes insipidus occurs if the lesions are bilateral It has been demonstrated that per

oxytocic activities of the neurohypophysis can be separated quantitatively[4, 43, 44, 4, 46]. One is justified, therefore, in referring to these substances as hormones. Although Van Dyke[4] believes in the chemical identity of the pressor and antidiuretic principles, others differ from this viewpoint. Kamm and associates[4] found that there was extremely little antidiuretic activity in purified oxytocic fractions but large amounts in potent pressor preparations. Furthermore, Gilman and Goodman[41] observed that antidiuretic activity is resistant to the action of certain reducing agents which destroy oxytocic activity. These studies indicate that the oxytocic principle probably is not concerned with antidiuretic activity. The relation of antidiuretic to pressor activity has been investigated by Heller[38] who noted that pressor activity was lost slightly more rapidly than antidiuretic activity during heat inactivation over a pH range of 0 57 to 10 0. This suggests that these two pharmacological effects likewise are due to separate principles.

Studies by du Vigneaud and associates (Irving and du Vigneaud[7], Potts and Gallagher[30], Stehle and Trister[8] and Stehle and Fraser[9]) have disclosed that molecules responsible for pressor and oxytocic activities contain amino acids joined in peptide linkage and that the presence of the intact peptide structure is essential for the pharmacological activity of these molecules. These two active principles appear to be polypeptides with molecular weights between 600 and 2 000[9, 30, 32]. They probably contain cystine, tyrosine and arginine and possibly also proline and leucine or isoleucine. These five amino acids account for only about 35 per cent of the molecules, assuming that only one molecule of each amino acid is present. Judging from this evidence there are no striking chemical or physical differences between the two principles. Cohn, Irving and du Vigneaud[46] have demonstrated that the pressor principle is definitely amphoteric with an isoelectric point at about pH 10 8 in buffers of 0 02 ionic strength, whereas a highly purified oxytocic preparation, which is also amphoteric, has an isoelectric point in the region of pH 8 5.

Physiology of the Neurohypophysial Principles

Elaboration of the Antidiuretic Substance by the Pituicytes

The known distribution of pituicytes in the neurohypophysis coincides exactly with the regions in which the antidiuretic substance has been localized by comparative anatomical, physiological and pharmacological investigations. That the active antidiuretic substance is not derived from the adenohypophysis was disclosed by studies of the hypophyses of the armadillo, chicken, sea cow and whale[6, 51, 3, 4, 5]. The glands of these animals are particularly adapted to such

ber of secretory pituicytes are destroyed suddenly Such a situation can be precipitated by subtotal neurohypophysectomy or by a piqure of the hypothalamus *which interrupts the innervation and thus the function of a comparable number* of pituicytes If there is sufficient secretory tissue left to engage in compensatory hypertrophy and this process must be going on during the so-called latent period the third phase of permanent polyuria does not occur If on the other hand compensatory hypertrophy fails to make up for this deficiency there supervenes a state of permanent polyuria which is due to an absolute insufficiency In this conception the latent period represents a phase during which compensatory metabolic adjustments occur The initial relative insufficiency may be compensated for by one of several mechanisms which would come into play during the latent period (a) reserve supplies of pitressin may continue to be secreted (b) the pituicytes may continue to function at a lower level after having been damaged partially by incomplete denervation (c) the pituicytes which are undamaged or remain innervated may hypertrophy (d) complete atrophy and absolute functional insufficiency of the pituicytes probably do not occur immediately after bilateral interruption of the supraoptico-hypophysial tracts It must take a few days for complete atrophy of the pituicytes to take place just as in the case of the gonads adrenal cortex or thyroid after hypophysectomy (e) compensatory physiological readjustments occur in other aspects of the body economy which have *to do with water exchange e g thyroid liver pancreas adrenal cortex etc* Thus the latent period represents a phase during which compensation for the initial insufficiency occurs If the original damage is extensive enough these compensatory mechanisms cannot obviate the development of an absolute deficiency of pitressin i e permanent diabetes insipidus The variability in the development of the experimental syndrome may be attributed to variations in the extent of *initial damage and the* success or lack of success of subsequent attempts on the part of the organism to compensate for it

Peripheral Effect of the Antidiuretic Substance and Its Clinical Significance

Burgess Harvey and Marshall[70] and Gersh[71] have demonstrated that the neurohypophysial antidiuretic substance acts directly on the renal tubules especially the descending loop of Henle when injected into an animal with diabetes insipidus The cells of this segment of the renal tubule are stimulated to reabsorb more water from the lumen of the tubules thus resulting in the retention of body water and a decrease in the urinary output The antidiuretic principle appears to reinforce and supplement the mechanism responsible normally for the reabsorption of approximately four fifths of the water that passes through the glomeruli[2]

manent diabetes insipidus results regularly, if the denervation, transection or ablation involves all or a major portion of the neurohypophysis, including the median eminence. Magoun, Fisher and Ranson[64] found that the onset of the disease could be prevented in monkeys if as little as 15 per cent. of the median eminence remained uninjured. Similar results have been recorded in rats[6] and dogs[6], although an equally precise localization has not been possible. In the rats polydypsia and polyuria result from ablation of the infundibular process or transection of the infundibular stem at the level of the infundibular process, and the intensity of the disorder increases in severity as the lesion is placed more centrally.

Pathological Physiology of Experimental Transient and Permanent Polyuria

Considerable confusion in the interpretation of experimental data has resulted because of the failure on the part of earlier workers to differentiate between permanent polyuria which represents true diabetes insipidus, and the transient type, which does not.

After the operative procedure, which is employed ordinarily to damage the hypothalamus, there is a transient state of polyuria lasting about one week. This is succeeded by a few days of normal fluid exchange. Within 10 or 12 days after operation, however, there appears the third or permanent phase of polyuria, which reaches its peak within two to three weeks postoperatively. The time extending from the day of operation to the day of the onset of the permanent polyuria is referred to as the latent period[60]. Most hypothalamic operations of the type which induces bilateral destruction of the supraoptico hypophysial tracts, are followed by these three phases of disturbance in water balance[58]. It has been observed also that experimental diabetes insipidus may develop gradually over a period of 2 to 3 weeks before reaching its peak. Heinbecker and Clark[63] have demonstrated, however, that the third phase of permanent polyuria may be achieved immediately after operation, if all of the neurohypophysial tissue is destroyed. These studies indicate that the extent of the damage to the secretory parenchyma of the neurohypophysis determines the subsequent course of the experimental syndrome. There have been many theories concerning the physiological significance of this sequence of events. So far as this writer can interpret the evidence, it indicates that the first phase of water disturbance is due to a state of relative insufficiency of pitressin and that the third phase represents a condition of absolute insufficiency. Ordinarily the organism has at its disposal certain reserve supplies of pitressin which contribute to the regulation of water metabolism in response to emergency demands, e.g. dehydration. A relative insufficiency in the supply of pitressin must occur when a significant proportion of the total num

sponse is not due to adrenalin or sympathin [1] whereas the latter shows that vagal impulses bring about the secretion of the pressor hormone of the neurohypophysis by way of the infundibular stem The pathway of the impulses engendered by vagal stimulation may be assumed from the foregoing as well as the following observations Electrical stimulation of the anterior part of the hypothalamus elicits a similar pressor effect but the reflex vagal pressor response is not obtained if the anterior part of the hypothalamus is damaged so that the connections between the supraoptic nuclei and the lobus nervosus are severed [5, 68] These observations were substantiated by Sattler who found this reflex absent in animals with experimental hypothalamic diabetes insipidus It may be assumed from these data that the afferent vagal impulses activate the supraoptic nuclei from whence the stimuli are transmitted to the lobus nervosus via the supraoptico-hypophysial tract That an identical pathway controls the secretion of the pressor and antidiuretic principles is suggested furthermore by correlation of the cytological condition of the pituicytes and the extent of the pressor effect elicited by vagal stimulation Repeated stimulation of the vagus results apparently in a loss of the secretory granules of the pituicytes coincidentally with a diminution of the pressor response Recovery of the pituicytes and reestablishment of the pressor response occurs after the stimulus is discontinued [1]

Evidence on the Neurogenic Secretion of the Oxytocic Substance

That the secretion of the oxytocic principle pitocin is also under the control of a hypothalamic mechanism has been disclosed by the experiments of Fisher Magoun and Ranson and Pencharz and Long Fisher and associates observed a marked disturbance in the parturition of cats afflicted with experimental hypothalamic diabetes insipidus Some of the animals died in labor others experienced a greatly protracted labor during which only part of a litter was delivered in some cases The adenohypophysis was found to be functionally intact in these animals Further evidence along similar lines has been recorded by Haterius and Ferguson [4] who showed that electrical stimulation of the infundibular stem enhances significantly the uterine activity of the rabbit in the post partum period This effect is abolished by transection of the infundibular stem but is not obviated by vagotomy splanchnicotomy or transection of the spinal cord

The atrophy, physiological inactivation or surgical destruction of the pituicytes is believed to result in a decrease in the concentration of the antidiuretic hormone in the blood. This results in diabetes insipidus, since the normal effect of this hormone on the water reabsorbing mechanism of the descending loop of Henle is interfered with. A disturbance of water metabolism in the opposite direction is induced by deprivation of water. Shortly after the latter is instituted, there is an appreciable decrease in the amount of antidiuretic substance stored in the infundibular process of the guinea pig, rabbit or rat[1c 3 4] and a coincidental hypertrophy and hyperplasia of the pituicytes[10]. Other studies indicate that these physiological and cytological changes are paralleled by an increase in the concentration of the antidiuretic principle in the circulating blood[1] and urine[40] of the rat.

Central Effect of the Antidiuretic Substance and Possible Clinical Significance Thereof

There is another aspect of the physiological activity of the antidiuretic hormone which is less clearly understood. This is its so called central effect which was demonstrated by Cushing[6] and Molitor and Pick[77] who observed a relatively stronger antidiuretic effect when the hormone was administered directly into the third ventricle or into the cerebellomedullary system. Other experiments seem to indicate furthermore that the antidiuretic activity of this hormone is inhibited by transection of the upper portion of the cervical cord[8 79]. These experimental observations are in accord with certain clinical data, viz. the relative therapeutic superiority of the nasal application of the hormone over that of the parenteral route and the absence of its antidiuretic action in certain cases of injury to the tuber cinereum or to the posterior region of the thalamus. Pathological changes with destructive lesions in these areas have been suggested in explanation of some of those rare instances of diabetes insipidus, which are partially or wholly refractory to the antidiuretic hormone[6 80 81 8 83].

Neurogenic Secretion of the Pressor Substance by the Pituicytes

In view of the possibility that the neurohypophysial hormone is a protein mother molecule from which three active principles may be separated by chemical means, it is significant that the same neurological mechanism seems to be concerned with the secretion of each of these various biologically active substances. The reflex vagus pressor response is elicited by afferent vagal impulses in animals subjected to transection of the cervical spinal cord but fails to occur if the infundibular stem is severed. The first observation indicates that the pressor re

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CHAPTER XV

DISEASES OF THE PARATHYROID GLANDS

By David P. Barr

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Structure and Functions of the Parathyroid Glands

Anatomy

The parathyroid glands are small bodies lying in close proximity to the thyroid. Their number is highly variable ranging from one to eight and even as in Erdheim's[45] case to twelve. Usually there are four arranged in two pairs. The superior or internal pair lie on the medial aspect of the dorsal surface of the thyroid at the junction of the upper and middle thirds of each lateral lobe. Although they ordinarily rest on the capsule of the thyroid gland, they may be imbedded sometimes in its substance. The inferior pair also known as the external glands likewise are on the dorsal surface farther down and closely associated with the inferior thyroid veins and the esophagus. When there are more than four parathyroid glands the accessory tissue may be scattered widely. As demonstrated by Ferry[136] it may be found on the anterior surface of the thyroid

It may be either in the anterior or posterior mediastinum or even imbedded in the thymus The size of the glands also is variable Cowdry[50] has stated that normally they may have measurements of 6 x 3 x 2 mm and a combined weight of 550 mg Biedl[14] has considered 3 to 15 x 2 to 4 mm as the limits of normal dimensions In the same individual the glands differ greatly in size

The blood supply of the parathyroids comes from both superior and inferior thyroid arteries and is very abundant It is returned through a venous plexus The innervation which seems to be scant comes from the perivascular sympathetic

Study of the minute anatomy of the glands has revealed densely packed columns and clumps of cells between which is a framework of connective tissue and a richly anastamosing network of capillaries Two types of cells have been recognized The chief cells have a relatively large vacuolar nucleus and pale cytoplasm which seldom contains granules The oxyphile cells are larger with small deeply staining nuclei and with granular cytoplasm readily stained by acid dyes It is said that before the age of ten only chief cells are found in human parathyroids[105]

Functions

It required many years and the work of a large number of observers to establish the importance and the various functions of the parathyroid glands The questions involved perhaps can be appreciated best by a brief account of the successive steps by which our present knowledge has been obtained The external parathyroid glands were described and named in 1880 by Sandstrom[125] and independently a year later by Baber[8] It is interesting that at almost the same time Weiss[142] in Billroth s clinic at Vienna found that the operation of thyroidectomy might be followed by serious and often fatal symptoms which were identical with the clinical condition known as tetany These two observations were not correlated Both Sandstrom and Baber believed that their newly discovered bodies were composed of embryonic thyroid tissue Their work attracted little attention and many years passed before the functional importance of the parathyroid tissue was realized It was indeed eleven years later that Gley[63] of Paris apparently unaware of the description of either Sandstrom or Baber rediscovered the glands He also considered that they were composed of thyroid tissue but was convinced by his experiments that they bore an important relation to the fatal symptoms which sometimes followed the complete extirpation of the thyroid gland

Gley was handicapped by his ignorance of the existence of the internal parathyroid glands which were described first by Kohn[82] four years later Without this knowledge the irregular results which followed thyroidectomy were difficult to interpret Kohn s discovery may have aided Vassale and Generali[140]

who demonstrated that removal of all parathyroid tissue even with preservation of the thyroid caused the death of an animal while the removal of the entire thyroid was not necessarily fatal if only one parathyroid was preserved They also showed that preservation of the parathyroid tissue did not prevent cretinism or myxedema With such experiments they were able to differentiate clearly between the functional characteristics of the two glands They showed also that the parathyroid glands were vital structures the removal of which was followed in 24 to 36 hours by changes in the excitability of nerves and muscles by twitchings stiffness and spasms which resulted in death in from five to ten days Except for this thoroughly demonstrated fact, the functions of the parathyroids still remained quite obscure

Investigations from this time followed two main hypotheses (1) that the parathyroids are important in the removal of toxins and particularly of the split products of protein, (2) that the glands are intimately associated with the regulation of mineral metabolism

Detoxifying Function of the Parathyroid Glands —Vassale and Generali attempted to explain the fatal symptoms of tetany by assigning to the parathyroids a detoxifying function It has been observed that a diet abundant in meat hastened the onset and increased the severity of the symptoms, also that parathyroidectomy was more fatal in young dogs and in pregnant animals in whom the metabolism was presumably high Biedl[34] noted that bleeding and transfusion of normal blood exerted a beneficial effect, while MacCallum[95] showed that the removal of blood and replacement with normal saline solution caused prompt relief of symptoms These observations seemed to lend support to the idea that tetany might be associated with a cumulative toxemia which might be due to split products of protein This hypothesis was followed with enthusiasm and for a time experiments seemed to furnish evidence of a detoxifying function Koch[67] believed that he could demonstrate methyl guanidine, a product of endogenous protein metabolism, in the urine of dogs after parathyroidectomy In a series of experiments Paton[113] showed that the symptoms produced by guanidine and methyl guanidine were identical with those which appear following thyroidectomy that small doses of these substances aggravated the symptoms of tetany, and that both guanidine and methyl guanidine were found in the urine and blood of parathyroidectomized animals These encouraging results did not, however long remain unchallenged It was realized by Paton himself, that the chemical methods available for the determination of guanidine in the blood and urine were unsatisfactory With an improved method Greenwald[68, 69] was unable to show any increase of these substances A closer analysis moreover, revealed that although there is close similarity between the symptoms produced by tetany and by chronic guanidine poisoning they are not identical

Recently the investigation of the detoxifying activity of the parathyroids,

while perhaps not entirely abandoned has received comparatively little attention The need of such an hypothesis to explain the origin of tetany has been removed largely by study of the changes in calcium metabolism which occur after parathyroidectomy

Functions of the Parathyroid Glands in Mineral Metabolism — It was shown by Sabbatini[1-4] that the injection of sodium citrate or sodium oxalate salts which precipitate calcium caused an increase in the excitability of nerve tissue and that the administration of calcium exerted a quieting effect Jacques Loeb[97] observed that the injection of any salt which precipitated calcium and diminished the amount of calcium in the circulating blood and fluids of the body caused twitching These experiments suggested that a lack of calcium in the body might be an important cause of the symptoms following parathyroidectomy MacCallum and Voegtlin[95] investigated the calcium metabolism of dogs after complete extirpation of the thyroids and parathyroids In the tetany thus produced they found a reduction in the calcium content of the blood amounting sometimes to as much as 50 per cent of the total Later MacCallum Lambert and Vogel[96] performed other important experiments using Abel s dialysis apparatus They perfused blood against an artificial fluid containing all the inorganic diffusible constituents of the blood except calcium and thus rid the blood of a large part of its calcium content This dialyzed blood deficient in calcium was perfused through an isolated extremity and produced excitability of nerves entirely similar to that observed after removal of parathyroids Luckhardt and Goldberg[99] and Salvesen[1-5] showed that parathyroidectomized dogs can be kept free from symptoms when sufficiently large amounts of calcium are administered

Following parathyroidectomy there is an immediate decrease in the phosphorus excreted in the urine followed by a rise in the level of serum phosphorus With this rise there is an almost simultaneous fall in serum calcium and a subsequent diminution of calcium excretion[7] Greenwald[66 67 70] has emphasized that the decrease in phosphorous excretion is much greater than can be accounted for by accumulation of phosphorus in the blood indicating a retention elsewhere in the body Bulger Dixon and Barr[30] found similar changes in a case of tetany which developed after removal of a parathyroid tumor

Parathyroid Hormone — By 1924 it was thoroughly established that removal of the parathyroid glands produced a hypocalcemia that this could be corrected and that tetany could be controlled by the administration of calcium It was during this year that Collip[38] presented final proof that properly prepared extracts of the parathyroid glands contain an active principle which uniformly relieves the symptoms in parathyroidectomized animals This can be accomplished even in young dogs kept on a meat diet the conditions which are most favorable to the development of fatal symptoms Collip also showed an elevation of the calcium content of the blood and a greatly increased excretion of calcium

who demonstrated that removal of all parathyroid tissue even with preservation of the thyroid, caused the death of an animal, while the removal of the entire thyroid was not necessarily fatal if only one parathyroid was preserved They also showed that preservation of the parathyroid tissue did not prevent cretinism or myxedema With such experiments they were able to differentiate clearly between the functional characteristics of the two glands They showed also that the parathyroid glands were vital structures the removal of which was followed in 24 to 36 hours by changes in the excitability of nerves and muscles by twitchings stiffness and spasms which resulted in death in from five to ten days Except for this thoroughly demonstrated fact, the functions of the parathyroids still remained quite obscure

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operations for recurrence in Grave s disease where scar tissue and adhesions have distorted the normal landmarks Tetany has been seen occasionally after laryngectomy for cancer when removal of surrounding structures has been unusually thorough

It may appear either because all of the parathyroid tissue has been removed a relatively uncommon occurrence because of the wide distribution of parathyroid tissue in man or because of interference with the blood supply Occasionally the vessels may be tied too completely at the time of operation More frequently they become obliterated gradually by fibrous tissue adhesions and contraction of scar tissue In such instances the symptoms of tetany may appear for the first time six weeks to two months after the operation

General — Parathyroidectomy is only one of the many causes of tetany The great variety of etiological relationships have been emphasized by Frankl Hochwart[61] in his elaborate monograph He showed that while the condition is met with at all periods of life it occurs most frequently in infants and young adults He also demonstrated the striking seasonal variation in its incidence and its surprising prevalence during the cold months from January to April His review revealed its relation to maternity especially to the late months of pregnancy and the period of lactation He also described and gave numerous examples of the occurrence of tetany in apparent epidemics in certain occupations in association with gastric and intestinal disorders accompanying or following infections and intoxications and associated with a variety of nervous diseases

Although none of these forms of tetany can be attributed directly to a lack of function of the parathyroids they are important because of the light which they cast on the pathogenesis of tetany and because any one of them may complicate the tetany of parathyroid origin or may indeed act as the precipitating cause of individual attacks

So called Epidemic Tetany — The incidence of tetany has varied greatly in different countries and cities In Vienna and Heidelberg there was for many years a prevalence so great as to suggest an epidemic character Particularly notable were the outbreaks in Vienna Young men between the ages of 17 and 25 were attacked by a tetany which occasionally was accompanied by fever and which subsided in two to three weeks Most astonishing was the incidence among workers in certain occupations In 399 cases collected from the literature by Frankl Hochwart 174 occurred in shoemakers and 95 in tailors Only 19 cases were seen in women The seasonal incidence was striking also a great majority of the cases appearing during the cold months and particularly in March and April Each year from August to October the condition disappeared almost entirely

It is significant as pointed out by Barker[7] that in the so-called epidemics of

in the urine. Administration to normal individuals, moreover, produces hyper calcemia and a condition which in many respects is the exact opposite of tetany. When it is continued in large doses, it is followed by serious consequences. Large amounts of calcium are removed from the skeleton with deposit in the kidneys lungs and stomach. Still larger doses cause violent toxic symptoms with congestion and hemorrhage in the gastrointestinal canal, cessation of renal function and death[45]

Tetany

Definition — Tetany is a condition characterized by hyperexcitability of the nervous system and by continuous or intermittent spasm of muscles. It follows the removal or functional insufficiency of the parathyroid glands but is associated also with a great number of clinical conditions which, to superficial examination appear unrelated. While it is convenient to consider tetany as a separate disease it is in reality, a physiological response of nerve and muscle tissue which appears inevitably whenever certain disturbances in calcium metabolism or acid base equilibrium occur in the animal organism.

History

The development of our knowledge of tetany has been reviewed interestingly by Barker. It appears that Clarke[43] in 1815 was the first to record the clinical features of the condition. In discussing spasm of the glottis in children he called attention to the rigidity of the extremities which accompany it. The name of tetany was given by Lucien Corvisart[49] who wrote a thesis on the subject in 1852. Erb[7] made his careful studies of the electrical hyperexcitability of the motor nerves in 1874 and the elder Chvostek[42] in 1876 described the facial phenomena which still bear his name. About 1880 great interest was aroused in Vienna by a prevalence of tetany which assumed almost epidemic proportions. At this time it was first noted by Weiss[14] that the clinical picture of tetany occasionally appeared after operations for the removal of goitre.

Etiology

After Thyroidectomy — In the early days of the operation tetany was seen most often in those cases in which complete thyroidectomy was performed for the removal of huge simple goitre. It is now encountered after complete removal of the thyroid for carcinoma of the gland but more often as an accident after subtotal thyroidectomy in cases in which the posterior capsule has not been conserved sufficiently. It is particularly liable to occur after secondary

operations for recurrence in Graves disease where scar tissue and adhesions have distorted the normal landmarks Tetany has been seen occasionally after laryngectomy for cancer when removal of surrounding structures has been unusually thorough

It may appear either because all of the parathyroid tissue has been removed a relatively uncommon occurrence because of the wide distribution of parathyroid tissue in man or because of interference with the blood supply Occasionally the vessels may be tied too completely at the time of operation More frequently they become obliterated gradually by fibrous tissue adhesions and contraction of scar tissue In such instances the symptoms of tetany may appear for the first time six weeks to two months after the operation

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tetany, patients, before the onset of contractures, had complained of paresthesias the actual spasms which led to the diagnosis appearing only under the influence of some infection, gastrointestinal upset or psychic trauma It was found also that some of the patients affected by seasonal tetany had suffered from laryngeal spasm or convulsions common manifestations of tetany in infancy

Tetany in Children — The study of tetany in children has emphasized many of the most important etiological factors It occurs chiefly during the winter months It is most prevalent among the lower classes and particularly in debilitated children The evidences of rickets are seldom absent Occasionally it may follow prolonged infections and more especially illnesses characterized by persistent diarrhea or excessive vomiting Gastric dilatation from obstruction of the pylorus is a frequent cause

Tetany in Pregnancy and Lactation — Trousseau[138] first described tetany in nursing mothers and gave to it the name of nurse's contracture' It is rare during the first months of pregnancy, at the time of labor or in the puerperium It appears usually in the latter half of pregnancy and may occur in the same individual with successive pregnancies, the interval being free of major attacks In the 52 cases collected by Frankl Hochwart, 39 occurred between January and April Children born of mothers with tetany may themselves exhibit the condition either immediately after birth or later

Tetany in Diseases of the Digestive Tract — Kussmaul[90] in 1869 writing of dilatation of the stomach recorded associated tonic spasms of the extremities This condition ordinarily due to stenosis of the pylorus, is known as *gastric tetany* It has been seen with the congenital pyloric stenosis of infants with the scars of old gastric or duodenal ulcers with peripyloric adhesions and cancer of the stomach It may occur from a dilated proximal pouch with hour glass contraction of the stomach It is interesting however, that only a relatively small number of patients who develop gastric dilatation ever show signs of tetany

Prolonged diarrhea often has been followed by muscular spasms both in children and in adults It has been described in association with sprue and in other diarrheas characterized by steatourhea[35, 50]

Tetany in Infections — Tetany is rare in acute infections although isolated examples of its occurrence have been recorded in a great number of diseases It has been observed most frequently perhaps after the long debilitating course of typhoid It has appeared usually in individuals who have been subject to attacks of tetany previous to the infection and has been seen most frequently in the winter months and in those localities where tetany is prevalent The circumstances clearly indicate that the infection furnishes only an exciting cause in a person who already is predisposed

Tetany in Nervous Disorders — More significant perhaps are the examples of tetany which have accompanied severe pain fear or other violent emotions

in hysterical or nervous individuals This form by no means is infrequent Anxiety preceding an ordeal such as an operation may be sufficient to produce it It is seen often in the early stages of anesthesia In hysteria and in epilepsy it has occurred during phases of excitement Tetany has also been seen during paroxysmal hyperpnea in patients convalescent from lethargic encephalitis[8]

Pseudohypoparathyroidism — Albright has called attention to a syndrome in which the clinical findings are those of idiopathic hypoparathyroidism but in which evidence suggests that the disturbance is not a lack of the hormone but a resistance to it Serum calcium values are depressed and serum phosphorus is greater than normal but the abnormal chemical findings fail to respond to the administration of parathyroid extract Study of the urine fails to reveal the usual *response of phosphate diuresis following the administration of parathyroid* extract[19]

Physiological Basis of Tetany

The multiplicity of etiological factors has introduced great difficulty in our understanding of tetany and for a long time it seemed impossible to present a unified explanation of all the apparently conflicting observations Our knowledge has been greatly advanced by the establishment of two fundamental facts

1 That there is a profound disturbance of calcium metabolism not only following parathyroidectomy but also accompanying several other forms of tetany

2 That changes in the acid base equilibrium of the body exert a controlling influence upon the excitability of nerves and muscles

Hypocalcemia in Tetany — The changes in calcium metabolism occurring after parathyroidectomy have been discussed already Hypocalcemia has been seen also in other forms of tetany in rickets in sprue in persistent diarrheas and in pregnancy

In none of these forms is there evidence of anatomical defect or functional insufficiency *of the parathyroid glands Indeed in rickets considerable hyper*plasia of the parathyroids usually is demonstrable Other explanations must be sought to explain the diminished blood calcium In pregnancy and lactation hypocalcemia appears to depend upon the great losses of calcium from the *mother in the formation of the child* A similar situation has been observed in the milk fever of high bred cows after calving A constant loss of calcium may be the ultimate explanation of hypocalcemia in long standing diarrhea The pathogenesis of the defect in rickets has been elucidated by the pediatricians who show the detrimental effect of lack of sunlight and insufficient content of vitamins in the diet Although none of the so-called epidemics of tetany have been studied from the standpoint of calcium metabolism it does not seem unlikely

that in these also hypocalcemia may be a feature and that food factors and lack of sunlight may play an important role in the greater prevalence of the disease during the winter months and the high incidence among tailors and shoemakers whose work keeps them throughout the year from exposure to direct sunlight

From these observations, one must conclude that whatever the cause of hypocalcemia may be, the result is hyperirritability of muscle and nerve tissue Since, in a number of the more important forms of tetany hypocalcemia is a striking feature, it is fair to assume that, in these cases, lowered calcium content is the controlling influence in the production of tetany This explanation does not, however account for many other examples of tetany which clinically cannot be differentiated from the hypocalcemic form

Acid base Equilibrium in Tetany —Our knowledge of tetany was aided greatly by an observation of Grant and Goldman[65] in Erlanger s laboratory They showed that tetany could be produced voluntarily in normal individuals by forced deep breathing By such overventilation carbonic acid is removed from the body to such an extent that the reaction of the blood and tissues become notably more alkaline In an experiment in which the subject breathed as deeply as possible at the rate of 14 per minute the reaction of the blood had changed in 25 minutes from pH 7 4 to pH 7 9 and spasms of hands and feet had appeared

It has been demonstrated since by Harrop[71] and by Healy [5] that the administration of sodium bicarbonate in amounts sufficient to alkalinize the blood may produce severe or even fatal tetany McCann[98] had suggested already in 1918 that gastric tetany might be due to the failure of the acid gastric secretion to pass into the duodenum

The production of tetany by means of increased alkalinity explains also the spasms which so often occur during the stage of early anesthesia and with pain fear or anxiety It is probably the cause of the occasional appearance of tetany in hysteria and epilepsy and certainly of its occurrence in the paroxysmal hyperpnea which follows epidemic encephalitis

Relation of Hypocalcemic Tetany to the Tetany of Increased Alkalinity — It is significant that the cases of tetany characterized by hypocalcemia may show little or no change in the alkalinity of the blood and that on the other hand, the patients with most marked alkalinity may exhibit an almost entirely normal calcium content The question arises whether these two types represent two entirely different causes for tetany or whether they may be in some way related It is known that the degree of ionization of calcium salts in the blood is dependent upon its alkalinity and that within the limits of change in the body the more alkaline the body fluids become, the less is the degree of calcium ionization The evidence indicates that the physiological functions of nerve and muscle are dependent upon the concentration of calcium ions, the value of which can be

diminished either by a reduction in the total amount of calcium in the blood (hypocalcemia) with normal alkalinity or by increased alkalinity with normal total calcium content It has been suggested therefore but without convincing evidence, that the tetany of alkalosis is in reality dependent upon reduction in the values of ionized calcium in serum and tissue fluids

The two factors may be combined temporarily or continuously in the same case and act upon each other to aggravate symptoms or precipitate attacks In parathyroid tetany spasms may be induced by voluntary overventilation Following complete removal of the parathyroids the violent attacks sometimes have been ushered in by periods of extreme hyperpnea Hysterical or highly emotional patients who are liable to spells of overbreathing may have been subjected to repeated pregnancies and prolonged periods of lactation or may have received insufficient sunlight and inadequate diet

Pathology

Pathological study of the parathyroid glands has been greatly hampered on account of their small size their hidden position the difficulty of their recognition and also because they are seldom examined during a routine autopsy Acute inflammation of the parathyroid glands themselves is unusual They have been involved by extension of inflammatory disease in surrounding tissues but in these instances symptoms of parathyroid insufficiency have not made their appearance In generalized tuberculosis and syphilis involvement of the parathyroids has occurred but has been unsuspected clinically and discovered for the first time at the post mortem examination

Hemorrhage into the parathyroid glands has been observed several times in patients who had died of infantile tetany The extravasation of blood has been of all grades from slight local leakage to extensive infiltration and obliteration of functional tissue Hemorrhages have been seen also in cases where tetany has not been noted clinically In the case of idiopathic tetany reported by Drake autopsy revealed fat replacement of all parathyroid tissue[64]

General Symptoms and Signs

The subjective and objective manifestations of tetany are always of the same general character whether they follow parathyroidectomy or voluntary forced breathing whether they are dependent upon a diminished amount of calcium in the blood or upon an increase in alkalinity The majority of the symptoms and signs of tetany are referable to the hyperexcitability of the nervous system While the motor nerves are involved most obviously the participation of the sensory apparatus is evidenced by parasthesias or pain and of the autonomic by

that in these also hypocalcemia may be a feature, and that food factors and lack of sunlight may play an important role in the greater prevalence of the disease during the winter months and the high incidence among tailors and shoemakers whose work keeps them throughout the year from exposure to direct sunlight

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Fig 2 A Photograph of patient with latent tetany following parathyroidectomy B Same patient showing typical facies in an attack induced by voluntary forced breathing

an abnormal sensitiveness to epinephrin and pilocarpin Differentiation should be made between *manifest tetany* in which the hyperexcitability is so great that intermittent attacks of muscular spasm occur spontaneously, and *latent tetany* in which no spontaneous motor phenomena are seen and which can be recognized only by special examinations



FIG 1 Complete left carpal pasm and stiffness of right hand in parathyroid tetany

Muscular Spasm —Attacks of tetany usually are preceded by parasthesias such as tingling or numbness of the fingers or lips There is often a feeling of anxiety and depression More rarely there may be headache vomiting or pain in the back Fibrillary twitching of the muscles is a frequent premonitory sign The spasms most often start in the hands and next involve the feet. They may, however, start in the muscles of the trunk or even in the facial muscles Usually the affection is symmetrical but it may involve one hand without being manifest elsewhere rarely it may be unilateral involving the arm and leg of one side and still more uncommonly it may be seen in the arm of one side and the leg of the

It has been observed that when a moderate spasm has been overcome by force a more powerful and violent after spasm may follow

Excruciating cramp-like pain may accompany the spasms in severe cases It usually appears and subsides with the contraction and in some cases may have an intermittent character when the contractions appear to be continuous Either direct pressure on muscles nerves and joints or movements of the muscles may cause great discomfort

During sleep the attacks of tetany usually are diminished but on the other hand occasionally they may appear for the first time in sleep

Mechanical Irritability of Nerves and Muscles —A great number of external stimuli have been observed to induce spasms of tetany in susceptible individuals. The administration of enemata a gastric lavage percussion of the abdomen pressure on muscles or nerves and temporary interference with the circulation of an extremity are among the many causes which have been mentioned Some of these are of such a striking character that they have been utilized in the clinical recognition of latent cases

Trousseau[139] pointed out in 1864 that if in latent tetany a tourniquet is applied firmly about the upper arm so as to suppress the flow of blood through the artery an obstetrical hand could be produced in a few minutes This is usually known as *Trousseau's sign* ' Three minutes or more of pressure may be necessary to elicit the sign even in susceptible individuals It is probably demonstrated best by the use of a blood pressure cuff The exact mechanism underlying this phenomenon has been under dispute The excessive irritability of nerves in tetany is admitted but it has been shown also that the excitability of nerves may be greatly exaggerated by partial anoxemia[103] Since the application of a tourniquet exerts pressure both on nerves and blood vessels it seems probable that both factors are concerned Frankl Hochwart s experiment[61] however seems to indicate that pressure on the nerve is entirely responsible He found that the slightest pressure applied to the exposed nerve of a parathyroidectomized dog caused spasm while even the strongest pressure upon the blood vessels was without effect When Trousseau s sign can be elicited it is a valuable diagnostic aid It is absent however in many undoubted cases of tetany

Chostek s sign may be demonstrated in the interval between acute attacks and also in latent tetany It consists of a localized spasm produced by percussion over a muscle or nerve Although this hyperirritability may be demonstrated in any part of the body usually it is shown best along the course of the facial nerve by tapping either at the stylomastoid foramen or on the cheek The sign may be seen in many patients who at the time present none of the other manifestations of tetany Unfortunately from a diagnostic standpoint it has been observed occasionally in Graves disease in tuberculosis and even in otherwise entirely normal individuals

other Many serious disturbances have been recorded Ordinarily when the trunk muscles are included in the spasm, those of the ventral aspect of the body are affected chiefly The head is bent forward, the sternomastoids are prominent and the chin may be drawn down until it touches the sternum If one sternomastoid is affected without the other, an appearance of torticollis may be produced Rarely the back muscles are affected more than the ventral group causing an opisthotonus which may be confused with tetanus In cases showing general involvement the diaphragm may become involved causing serious interference with respiration The tongue not uncommonly is included and causes a thick speech Strabismus may be a prominent and troublesome symptom In children and occasionally in adults the muscles of the larynx are involved giving rise to laryngismus stridulus or croup

While any muscle may be affected and the vagaries of involvement are considerable, certain types of contraction occur so frequently that they must be given special emphasis and description

Carpopedal spasms are seen in many rachitic infants in whom other evidences of the condition never become manifest Usually they are the earliest and probably are the most constant of the major phenomena in adult forms of tetany (Fig 1) In the hand the thumb is adducted in close contact with the index finger or flexed into the palm beneath fingers which are flexed in the metacarpophalangeal and extended in the interphalangeal articulations The outer and inner borders are approximated producing a hollowing of the palm The shape of the hand resembles so strikingly that which the obstetrician employs in his examination that it was called by Trousseau the 'main de l accoucheur' Other attitudes of the hand may be encountered but rarely Mention may be made of the hand which assumes the shape of a bird s claw, of that which is flexed in all its joints producing a tightly closed fist and a contracture which may be so marked that the fingernails cause necrosis of the palm, and of the extremely uncommon attitude in which all the fingers are spread wide apart and extended

The pedal spasm usually consists of powerful flexion and adduction causing extreme arching and concavity of the sole The foot is extended at the ankle and inverted Russell[123] states that dorsal flexion of the foot at the ankle has been observed

When the spasms become general, the face is involved Often this is limited to a feeling of stiffness about the mouth and to a fibrillary contraction or twitching of the muscles at the corners of the mouth In more severe cases the face is contorted into a ghastly grin in which the eyes are closed and the angles of the mouth are drawn up and outward (Fig 2)

During the spasms the muscles are hard and firm, and considerable force is necessary to release them This may be noted by the patient, as when a porter carrying suitcases finds himself quite unable to release his grasp on the handles

have completely formed there is hypoplasia which leaves its scars in the tooth structure as pit like depressions extending horizontally across the surface If the disease develops after the age of twelve the tooth structure may be normal except for blunting of the root ends and hypoplasia of the last teeth to form

Bilateral cataracts tend to form in all cases of long standing Usually these are subcapsular opacities which can be detected only with the slit lamp In other cases however there is transformation of both lenses into gray white masses which require surgical removal for the restoration of eyesight

Prognosis

Fortunately complete removal of parathyroid tissue in man always has been infrequent Many of the patients who formerly developed tetany after thyroid operations made a more or less complete recovery although latent tetany and nutritional disturbances often persisted In those rare cases where the parathyroids were entirely extirpated death was inevitable from the violent symptoms which appeared immediately after the operation Those who retained some but insufficient parathyroid tissue had a miserable existence in which a constant tendency to seizures precluded all normal activity and led to pitiful anxiety or profound depression With our present methods of treatment patients may survive even complete parathyroidectomy and if calcium is maintained at a normal level in the serum may escape the discomforts and the serious trophic disturbances of chronic hypoparathyroidism

Treatment

General — The treatment of tetany varies greatly with the underlying cause and with the mechanism involved To control the spasms in cases dependent upon hypocalcemia and disturbed mineral metabolism the chief efforts must be directed to an attempt to increase the content of calcium in the circulating blood For patients whose tetany is the accompaniment of increased alkalinity measures devised to change the reaction of the blood should be most effective In cases associated with disturbance of calcium metabolism the initial cause of hypocalcemia is of great importance When it has developed from lack of sunlight or an insufficient intake of vitamin D administration of these agents in moderate amounts may be sufficient to remove the tendency If it is dependent upon absence or insufficiency of the parathyroid glands parathyroid hormone or very large doses of vitamin D or both may be required in the management of the acute attack During maternity and in continuously undernourished individuals a supply of extra calcium sometimes is quite as significant as an increase in vitamin content It should be remembered that several different factors may be of importance in the same case as when overventilation occurs with hypocalcemia or

Other tests, depending upon the mechanical irritability of nerves have been described by Pool[117] and by Schlesinger[127] They consist of the production of carpal spasm by forcible abduction of the arm and of pedal spasm by flexion of the trunk upon the thighs with legs extended They probably parallel the positive response to Trousseau's sign and in general have the same significance

Electrical Irritability of Nerves and Muscles — Erb[67] of Heidelberg was the first to demonstrate the utility of electrical excitability as a diagnostic test in tetany It has been studied since quantitatively and with great care by von Pirquet[115] and many others The chief abnormality in tetany consists of a response to a current much smaller than that required to stimulate a normal individual In children cathodal opening contractions are apparent with a current usually much less than 5 milliamperes which is considered the least which will stimulate normal nerves By von Pirquet anodal opening contractions with currents feebler than 5 milliamperes have been considered also indicative of mild tetany These electrical tests, when performed with experience and judgment have been of great aid in the recognition of latent tetany in children

Reflexes in Tetany — Considering the extreme hyperexcitability of muscles and nerves exaggeration of reflexes might be expected It is surprising that this does not occur with any regularity The knee jerks are normal in some cases, exaggerated in others and may be greatly diminished or actually not obtainable

Mental and Nervous Symptoms — The state of chronic tetany not infrequently is associated with profound anxiety and depression or by a sense of impending disaster Frankl Hochwart[61] collected examples of the occasional occurrence of psychopathic symptoms varying from transitory delirium during the individual attacks to confusion and actual dementia

Epilepsy or epileptiform attacks have developed not infrequently in tetany The cases collected by Redlich[119] indicate that the association of the two conditions is not limited to any particular form of tetany The convulsions have been seen not only after thyroidectomy but also in association with maternal and gastric tetany They are most frequent in the tetany of young children and with long continued hypocalcemia Very rarely chronic tetany has been accompanied by papilledema engorgement of retinal veins and increased cerebrospinal pressure of a degree to suggest the presence of brain tumor[31]

The mechanism of the nervous symptoms is not clear Edema of the brain itself[1] or increase in cerebrospinal fluid has been suggested Of great interest is the symmetrical calcification of basal ganglia and other parts of the brain which has been demonstrated by Eaton[65] and others[18]

Other Manifestations — Falling nails and loss of hair have been mentioned as consequences of hypoparathyroidism[78] More established are enamel defects of the teeth, which occur both in experimental tetany and in long continued hypocalcemia in man When hypoparathyroidism develops before the teeth

accomplishes an elevation in the level of blood calcium depending upon the size of the dose and the condition of the patient Following subcutaneous or intra muscular injections the serum calcium begins to rise in about 4 hours reaches its maximum in from 12 to 18 hours and returns to the previous level in about 20 to 24 hours It has been shown that the first demonstrable effect of the hormone is an immediate increase in the phosphorus excreted in the urine the second effect is a fall in the level of phosphorus in the serum and an almost simultaneous rise in serum calcium and finally there is an increased excretion of calcium in the urine In not a few patients the subcutaneous use of the preparation produces painful local reactions These consist of red hot areas of induration and edema at the site of injection which usually appear one to two hours after the puncture and gradually disappear over a period of several days Their size varies from an inch to several inches in diameter They are most disturbing factors in those patients requiring frequent injections Tolerance may be acquired and the necessary dose in some cases has become so high as to offer insuperable difficulties in administration and to constitute an unbearable expense to the patient In Lisser s case[91] enormous doses were ineffective finally in controlling symptoms

2 *Calcium Administration* —Luckhardt and Goldberg[93] Salvesen[125] and others showed that parathyroidectomized animals may be kept alive and even in good health if calcium salts are administered in sufficient amounts Immediate relief of the symptoms of acute parathyroid tetany have followed the intravenous use of calcium Clinically three calcium preparations are commonly employed Calcium lactate usually is administered by mouth It is non irritating and may be taken in large amounts the ordinary dosage being 1 0 to 2 0 gm repeated frequently and in severe cases as often as every two hours Calcium chloride also may be given by mouth in dilute solution but it is irritating and apt to cause nausea and gastric distress It cannot be used subcutaneously as it produces intense pain and extensive necrosis Its chief use is as an intravenous preparation which may be administered in doses of 1 0 to 2 0 gm in 5 per cent solution It should be injected slowly because of the toxic effect of high calcium concentration upon heart muscle and with great caution to avoid infiltration of the tissues about the vein Because it is an acid salt it serves when tolerated the double purpose of supplying calcium and of reducing alkalinity The beneficial effect of intravenous calcium chloride upon spasms due to hypocalcemia sometimes is dramatic and almost immediate Calcium gluconate has a similar action and is used more often since it may be given both by mouth as well as by intramuscular and intravenous routes since it is relatively non irritating to tissues and since it possesses many of the advantages of calcium chloride Its dosage is the same as calcium chloride For parenteral use a 5 per cent solution usually is employed

3a *Dihydrotachysterol* — Fortunately the correct use of activation products of ergosterol in the treatment of hypocalcemic tetany has made unnecessary the

when a patient whose parathyroids have been removed by operation is deprived of sunlight and fails to take an adequate diet

Correction of Alkalosis — When tetany follows excessive breathing, whether this be voluntary or the accompaniment of disease there is an increased alkalinity which has resulted from loss of carbon dioxide To correct this the most direct as well as the most effective method is the administration of carbon dioxide in the inspired air In high percentages this gas is toxic and may be dangerous In 5 to 7 per cent mixtures with oxygen it is a powerful stimulant to the respiration but has no deleterious effects Holding the breath will allow carbon dioxide to accumulate in the body and in the control of acute spasms may be all that is required It produces however an anoxemia which in itself increases the irritability of nervous tissue In those cases where overventilation tends to recur or where it is a complicating factor in some other form of tetany, carbon dioxide oxygen mixtures may be inspired through a mask or from a tent Special tanks containing 5 per cent carbon dioxide in 95 per cent oxygen and equipped with reducing valves are now generally available Lacking them, the carbon dioxide may be inspired by means of an extremely simple method A newspaper can be made into a funnel the small end of which is made to fit around the nose and mouth of the patient Air breathed in from this funnel will contain from the last expiration a considerable amount of carbon dioxide the percentage of which will vary up to 4 0 per cent with the volume of the funnel and the snugness with which the funnel is fitted to the face

Another method of diminishing alkalinity is by means of the administration of fixed acids For this purpose the acid salt ammonium chloride is perhaps the most effective drug It can be administered in tablets by mouth in doses of 1 0 to 2 0 grams It is irritating to the stomach if given over any considerable period In animals McCann[98] has given ammonium chloride intravenously in 0 822 per cent solution

Correction of Hypocalcemia — This may be accomplished or aided by the use of (1) parathyroid injection (2) calcium salts and (3) two activation products of ergosterol dihydrotachysterol and calciferol (crystalline vitamin D_2)

1 *Parathyroid Injection* — The active principle of the parathyroid glands can be isolated from the parathyroids of an ox It is obtainable in conveniently and accurately standardized form under the pharmacopeial name of parathyroid injection, one c c of which possesses a potency of not less than 100 U S P parathyroid units each unit representing one one hundredth of the amount required to raise the calcium content of 100 c c of the blood serum of normal dogs 1 mgm within 16 to 18 hours after administration It is inactive by mouth but is active when given subcutaneously or intramuscularly Reactions simulating those from injection of foreign protein and sometimes quite severe have followed its intravenous use The injection is not accompanied by any important sensations but

properly treated may result fatally The situation constitutes an emergency which demands thorough and careful treatment The seriousness of the condition cannot be judged entirely by the character of the spasms Sometimes they yield to the simplest measure such as holding the breath or the administration of carbon dioxide and the subsequent use of calcium by mouth In other cases the underlying state is so severe that its control taxes every therapeutic resource In the emergency chief reliance must be placed on measures which produce prompt effects on the level of serum calcium The action of dihydrotachysterol and calciferol is too long delayed to serve the immediate purpose If the spasms are violent and continue in spite of the administration of carbon dioxide, calcium chloride or calcium gluconate should be given intravenously At the same time parathyroid injection may be given intramuscularly Large doses may be required and 100 to 300 U S P units (1 0–3 0 c c) or even more have been given in severe cases Beneficial effect as evidenced by an elevation of serum calcium usually is apparent within a few hours and reaches a maximum in 8 to 18 hours For maintenance of the level of serum calcium in average adult dose is 20 to 40 units (0 2 to 0 4 c c) every 12 hours Continuation of hormone therapy is however undesirable and an effort should be made to substitute calciferol as soon as possible It is desirable therefore to administer orally 20 to 30 mgm (800 000 to 1 200 000 international units) of calciferol at the same time the parathyroid injection is started This may be repeated every 24 hours until the calcium in the serum has attained a normal level

In the treatment of severe attacks of true hypoparathyroid tetany there is little immediate danger of overdosage either with parathormone or with the derivatives of ergosterol If however the diagnosis is incorrect and the tetany has arisen from causes other than hypocalcemia the possibility of harm from large doses of these extremely potent chemicals is considerable In any case frequent determinations of serum calcium are desirable during the early stages of the management If this is not possible the urine should be tested by the Sulkowitch reagent[18] a solution containing oxalate radicals buffered at such pH that when an equal amount of the reagent is added to urine the calcium will come down almost immediately as a fine white precipitate of calcium oxalate If there is no precipitation by this test the urine contains no appreciable amount of calcium and it may be assumed that the serum calcium does not exceed 5 to 7 5 mgm per 100 c c If there is a fine white cloud there is a moderate amount of calcium and the level of calcium in the serum probably is within a satisfactory range If the precipitate looks like milk there is danger of hypercalcemia The Sulkowitch test is a great aid in the practical management of patients with tetany

After the acute attack has been controlled and the aim of treatment is the establishment and maintenance of normal conditions calciferol is the drug of choice The maintenance dosage must be determined for each individual and

long continued employment of parathyroid injection It had long been known that tetany arising from lack of sunlight and insufficient or improper diet in rickets, pregnancy, lactation and chronic undernutrition could be corrected by the use of cod liver oil *Later the same results were obtained by the use of purified* preparations of fish oils containing a higher concentration of vitamin D It was disappointing to find, however, that dosage sufficient to correct rickets had relatively little effect upon hypocalcemia from hypoparathyroidism or from any causes other than lack of vitamin D For our knowledge of the usefulness of dihydrotachysterol we are indebted to the work of Holtz[79], who studied with Windaus in Gottingen the effects of various fractions of irradiated ergosterol upon calcium metabolism In the course of his researches he found that three sterols caused definite elevation in the level of serum calcium These were fractions known as tachysterol, toxisterol and the one believed to be vitamin D itself Of these, tachysterol was thought to be least toxic and was rendered still less injurious by the synthesis of a dihydro derivative *With small doses of di*hydrotachysterol by mouth Holtz found it possible to relieve tetany and to maintain the serum calcium at normal levels in parathyroidectomized animals He also found it effective in the treatment of idiopathic hypocalcemic tetany and in the hypoparathyroidism following thyroid operations The substance was introduced under the name of A T 10 (anti tetany preparation No 10) and became commercially available in an oil solution in which 1 0 c c contained 5 mgm of a basic substance approximately 2 mgm of which was pure dihydrotachysterol This can be given orally in doses of 0 5 to 2 0 c c each day Although dihydrotachysterol alone will raise the serum calcium to normal the amount that is required for maintenance of normal levels of serum calcium is less when calcium salts are used as *an adjuvant With an average normal diet daily doses* of from 1 to 2 c c are required but when this is supplemented by 4 0 to 10 0 gm of calcium lactate or calcium gluconate each day the dosage can be reduced to 0 3 to 1 0 c c The effect of dihydrotachysterol on serum calcium is not immediately apparent Usually the first increase appears in about 48 hours With small doses normal levels may be expected in most cases of hypoparathyroidism within 7 to 14 days

3*b Calciferol* — Fortunately it has been found that calciferol (crystalline vitamin D_2) produces the same effects as dihydrotachysterol on the level of serum calcium and consequently upon hypocalcemic tetany when given in equivalent doses McLean[100] found that 1 c c of A T 10 (approximately 2 mgm of dihydrotachysterol) is therapeutically equivalent to 10 mgm (400 000 international units) of crystalline vitamin D_2 This preparation may be given also by mouth Like dihydrotachysterol its action is delayed the first increase in the level of serum calcium usually is not observable before 24 hours have elapsed

Treatment of Parathyroid Tetany — About 24 hours after the removal of an excessive amount of parathyroid tissue symptoms of tetany appear which, if not

thyroidism and by Wilder and others served to indicate the chief features of the condition and to establish a clinical syndrome

Etiology

Hyperparathyroidism may be produced at will by the injection of parathormone as has been demonstrated experimentally in animals It may occur clinically as a consequence of neoplasm or hyperplasia of the parathyroid glands The great majority of the cases occurring spontaneously have been associated with a single adenoma a few with more than one adenoma and a small group reported by Albright and his associates[16] with diffuse hypertrophy or hyperplasia of all parathyroid tissue Albright[17] has reported a case in which persistent low phosphorus rickets was accompanied also by massive calcium deposits in the kidneys hyperchloremia and low serum bicarbonate level A similar situation was recorded by Butler[28] All of these cases may be regarded as examples of *primary hyperparathyroidism* in the sense that the clinical syndrome depends upon an excess of parathyroid activity for which no adequate explanation can be offered Many of them have been accompanied by decalcification of the skeleton and by the deformities of generalized osteitis fibrosa cystica of von Recklinghausen[118] These osseous changes must be regarded as secondary since they may be closely simulated by the skeletal lesions of hyperparathyroidism produced experimentally in animals[84, 85] The primary disease has been observed in young children and in one infant only three months of age[23]

In a great variety of conditions hyperplasia and occasionally tumors of the parathyroids seem to be secondary to changes elsewhere in the body Under such circumstances a state of *secondary hyperparathyroidism* may be said to exist In animals Erdheim[69] found hyperplasia in the artificially produced rickets of rats Marine[104] demonstrated it in fowls which were kept on a low intake of calcium Higgins and Sheard[78] noted it when sunlight was deficient After extirpation of a part of the parathyroid glands there is a compensatory hyperplasia of the remaining tissue Hyperplastic changes were demonstrated by Ritter[112] and later by Pappenheimer and Minot[109] in human rickets MacCallum[94] Bergmann[22] and Albright[7] reported parathyroid hyperplasia in human nephritis More recently the associations of parathyroid function and nephritis have been explored further by Pappenheimer and his associates[110, 111] Apparently hyperplasia of the glands and possibly hyperparathyroidism also develop secondary to diverse skeletal diseases that include not only osteomalacia or adult rickets but also osseous metastases from mammary cancer and multiple myeloma[29] Tumors of the parathyroid glands have been observed also in association with Cushing's disease[107]

The mechanisms by which the parathyroids are stimulated in nephritis are

varies widely From 60 000 to 400 000 international units of vitamin D may be required each day The vitamin will maintain normal levels of serum calcium with an average normal diet, but the dosage often may be decreased 50 to 60 per cent by the addition of 4 to 10 gm of calcium gluconate to the daily intake Milk is to be avoided because of its high phosphorus content Aub[3] has shown that in patients with parathyroprivic tetany, who are receiving adequate intakes of calcium, the use of thyroid tends to cause elevation in serum calcium and to increase the excretion of phosphate The excretion of calcium is augmented after approximately normal calcium levels in the serum have been attained Thyroid in appropriate doses, therefore, may be indicated in parathyroid tetany even in patients who present no striking evidence of hypothyroidism

Hyperparathyroidism

Definition — Hyperparathyroidism is a condition resulting from excessive parathyroid secretion It is accompanied by hypercalcemia, hypophosphatemia, diminished excitability of muscles and changes in the bones, ordinarily it is associated with tumors or hyperplasia of the parathyroid glands

History

Parathyroid tumors and enlargements have been recognized since 1899 when Kocher[88] suggested such an origin for five glycogen containing tumors which he had observed in the region of the thyroid The association of parathyroid tumors with von Recklinghausen s osteitis fibrosa cystica was noted by many observers[4, 81, 78] It was not realized, however that enlarged parathyroid glands might be functionally significant before 1924, when the discovery of an active parathyroid hormone by Collip[14, 15] made it possible to study hyperparathyroidism experimentally

Two years later Du Bois[7] and Aub[32] studied calcium and phosphorus metabolism of a patient with von Recklinghausen s disease of bone The metabolic changes resembled those following injection of parathormone A diagnosis of overactivity of the parathyroid glands was made, and in April 1926 the neck was explored with the idea of correcting the metabolic disorder by resection of para thyroid tissues Removal of two parathyroid glands failed to benefit the patient, and it was not until several years later that a tumor of an abnormally placed parathyroid gland was located and removed In the meantime Mandl, a surgeon of Vienna, operated upon a patient with the same type of bone disease and re moved a parathyroid tumor The operation was followed by clinical improvement and partial correction of the bone defect Following this the study of similar cases by Gold by Barr and Bulger, who first used the name of hyperpara

characteristic but less constant are the fibrosing osteitis in which fibrous tissue replaces bone with formation of encapsulated fluid filled cysts and the collections of osteoblasts and osteoclasts which in the past have been known as benign giant cell tumors or osteoclastomes. These form most often in the long bones but may involve the jaw (Fig. 3), the pelvis, the ribs or even the bones of the head. The extent to which the osseous lesions may progress is well shown in the skeletons studied by von Recklinghausen[118] and by Schonenberger[119]. Microscopically the swellings show hemorrhages which in some cases seem to dominate the picture. There is extensive fibrosis in which a great number of giant cells may be found (Fig. 4). Considerable difference in opinion exists as to the cause of the skeletal lesions of hyperparathyroidism, one school believing that the decalcification of bone is due to a direct action of parathyroid hormone on bone[101] and the other holding that the changes in the skeleton are secondary to factors which cause loss of calcium from the body[15]. Whatever may be the explanation, there is an increased absorption of bone which causes weakening of osseous structures with hemorrhages and fractures. It does not interfere with the processes of repair and injuries of bone are followed by intense osteoblastic activity as well as by increase in stroma of the bone marrow and fibrosis. The concurrent osteoblastic and osteoclastic activity in the skeleton account for many of the variations in the clinical picture.

In hyperparathyroidism secondary to nephritis extensive osseous lesions have been observed. When the nephritis develops in childhood and when the bones are undergoing endochondral ossification, a condition known as renal dwarfism may occur[11]. Bones are decalcified and deformed and skeletal growth is retarded. In some cases[111] there have been no demonstrable bone changes. This is ostensibly due to an intake of calcium as with great milk drinking which is sufficiently high to keep up with the excessive output.

Teeth. — Cysts or tumors of the jaw may cause malocclusion or distortion of the normal arrangement of the teeth. Considering the extensive changes which occur in osseous tissue it is remarkable that even in extreme cases of demineralization there is no increase in dental caries. This seems to indicate that the resorption of calcium and phosphorus from mature teeth does not occur by way of the blood stream[115].

Metastatic Calcification. — In several cases a remarkable deposit of calcium has been found in the soft tissues. The alveolar walls of the lungs, the glands of gastric mucosa and the convoluted tubules of the kidneys have been involved most often and it is probably significant that these are the places where acids are excreted from the body. Metastatic calcification has not, however, been limited to these locations. Dawson and Struthers[31] found calcium infiltration of practically every organ. Peneke[114] in a case complicated with chronic nephritis found calcification in the left heart, the smaller arteries, the thyroid, the spleen and

not thoroughly understood There is, however, much evidence to support the idea that retention of phosphates is the probable cause, and it is significant that Drake[53] was able to produce parathyroid hyperplasia in rabbits by parenteral administration of phosphates Others however have suggested that low serum calcium[16] or a change in the calcium and inorganic phosphorus equilibrium is responsible[112] The etiology of secondary hyperparathyroidism recently has been well reviewed by Anderson[2?]

The possibility of a combination of primary and secondary hyperparathyroidism exists when renal lesions consequent to primary hyperparathyroidism stimulate the glands to still greater activity Cases in which this situation has developed have been reported by Soffer and Cohn[134] and by Downs and Scott[5]

Pathology

Parathyroid Hyperplasia and Tumors — The pathology of the parathyroid glands has been studied extensively by Castleman and Mallory[39,40] and by Hunter and Turnbull[82] Adenomas usually weigh from 0 5 to 20 gm, but one weighing 101 gm has been reported[133] Most of them are composed predominantly of chief cells but in rare instances oxyphile cell tumors[141] have been described Malignant tumors as a cause of hyperparathyroidism are excessively rare[6] In the case reported by Meyer Rose and Ragins[106] hyperparathyroidism polycystic disease and nephrolithiasis were dependent upon a carcinoma of the parathyroid, removal of which caused only temporary improvement with later recurrence and malignant metastases

In 162 cases of hyperparathyroidism reviewed by Castleman and Mallory 128 showed a localized growth in a single parathyroid gland, 12 showed localized growths in more than one gland while 22 showed diffuse hyperplasia of all glandular tissue In 2 of these the hyperplasia seemed to be of chief cells The remaining 20 presented a remarkable picture characterized by cells of enormous dimensions containing large amounts of clear lightly staining cytoplasm In such cases at the Massachusetts General Hospital the total amount of parathyroid tissue was 40 to 100 times normal and individual cells had a radius 5 times normal and volume 125 times normal suggesting that the process might represent hypertrophy rather than hyperplasia

The change in the glands in renal hyperparathyroidism appears to be a true hyperplasia affecting all glands but not to the same degree Enlargement may be great and a single gland may attain a size of 5 gm

Changes in the Bones — Decalcification of the skeleton is the most constant osseous manifestation This is attributable to the hyperparathyroidism It is not related directly to rickets or to osteomalacia although possibly in some cases the hyperparathyroidism has been complicated by these conditions More

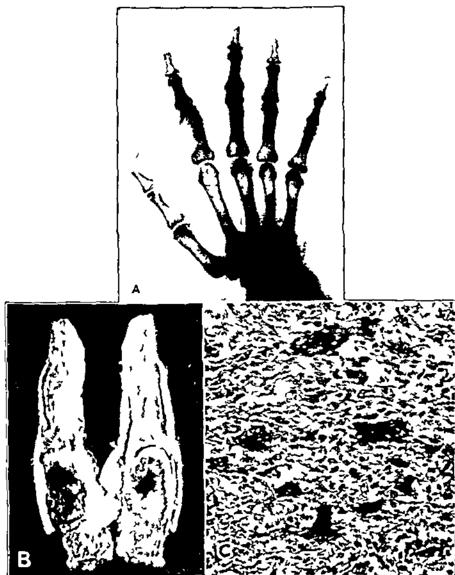


Fig 4 A X ray showing giant cell tumor of first phalanx of fore finger
B Longitudinal section through amputated finger showing gross appearance of the tumor
C Microscopical appearance of tumor showing fibrosis and giant cells.

skin as well as in the walls of a parathyroid tumor Most significant is the occurrence of metastatic calcification in the experimental condition produced by excessive dosage of parathormone In the hyperparathyroidism secondary to renal disease there may be most extensive calcification of the arteries[77], calcification of the skin[116] or calcification about joints[10]



Fig 3 Case of hyperparathyroidism (Barr and Bulger showing tumor of left maxilla abnormal mobility of joints and extreme flabbiness of muscles

Nephrolithiasis — Because of the increased urinary excretion of calcium and phosphate patients with hyperparathyroidism are predisposed to the formation of urinary calculi of calcium phosphate or of calcium oxalate Renal stones have been a feature in about 70 per cent of the cases Obstruction and infection secondary to nephrolithiasis are common and account for many of the deaths

tion[74] In one of the cases described by Barr and Bulger (Fig 3) the muscular weakness was combined with an abnormal mobility of joints

Genitourinary Symptoms — Complaints referable to the urinary tract may be the first to call attention to the disease Albright[18] has emphasized that these may be dependent upon three types of lesion (1) pyelonephritis secondary to the formation of calcium phosphate stones (2) nephrocalcinosis in which calcium deposits in renal parenchyma are predominant (3) acute parathyroid poisoning with calcium deposits in the kidneys as well as in other organs The symptoms associated with the formation and development of stones in the pelves or ureters are the same as those from nephrolithiasis of any origin Due to irritation or infection of the bladder frequency of urination may be an early symptom Polyuria may occur even in patients whose renal function otherwise appears to be normal It may be so marked as to suggest diabetes insipidus There may be intermittent attacks of pain Renal insufficiency may occur from hydronephrosis or from pyelonephritis in association with stones or from extensive renal calcinosis

Circulatory Symptoms — Cardiac irregularities and conduction defects have been noted[46] High blood pressure may or may not accompany the renal insufficiency of the disease[132, 137]

Hematological Manifestations — Because of extensive fibrosis of the bone marrow anemia and leucopenia have been encountered occasionally in hyperparathyroidism Increased viscosity of the blood which is seen when excessive amounts of parathormone are given experimentally is not often a feature of clinical cases

Gastrointestinal Symptoms — Many patients complain of constipation and flatulence and some have nausea with attacks of vomiting

Parathyroid Tumor — Occasionally a parathyroid tumor may be palpated in the region of the thyroid gland The chance of doing so is enhanced by asking the patient to swallow while the neck is being felt More often no tumor is identified even when the swelling is of considerable size The usual position of the parathyroid glands posterior to the thyroid makes palpation difficult Differentiation from thyroid adenoma cannot be made accurately Furthermore a number of tumors have arisen from one of the inferior glands which may lie beneath the clavicle or sternum while still others are in the anterior mediastinum lying upon or imbedded in the thymus gland

Hypercalcemia and Abnormalities in Calcium and Phosphorus Metabolism — Jacoby and Schroth[58] were the first to investigate the calcium metabolism in osteitis fibrosa cystica Mandl found an increased excretion of calcium in the urine, which was reduced to one sixth of the original amount following the removal of a parathyroid tumor[103] Subsequent studies by many observers have established an abnormally high excretion of calcium in the urine as a feature,

from the disease Calcium salts may be deposited also in the renal parenchyma as a form of nephrocalcinosis which leads to inflammatory changes, sclerosis and contracted kidneys Acute poisoning with parathormone may be associated with extensive calcium deposits in the kidney and other organs[11, 12]

Clinical Features

Pain — The most prominent symptom in active hyperparathyroidism is pain This may be intensified by weight bearing It is referred by the patient to the bones and joints and may simulate the distress of early arthritis At other times it has been mistaken for a polyneuritis

Other Symptoms Referable to the Bones — Cysts or giant cell tumors may occur in any bone (Fig 4) but are most frequent in the femur and humeros They often appear at the site of an injury The pulling of a tooth may be followed by a progressive swelling of the jaw or a relatively slight blow may cause the development of a tumor on one of the long bones Although pains in the bones and muscles are not uncommon, the swellings themselves usually are painless When covered by heavy musculature as in the thigh, they may be entirely unsuspected, until a pathological fracture calls sudden attention to their presence

Stooping due to an increasing kyphosis and bowing of the legs may be noticed by the patient or his friends Sometimes there is a startling loss of height as in the patient described by Hannon, Shorr McClellan and Du Bois[73], who shrank more than four inches

X ray of the bones reveals localized cysts and tumors with marked thinning of the cortex (Fig 4) It also shows in most cases a somewhat irregular rare faction and in advanced cases an abnormal bending of weight bearing bones The femurs and to a less extent the tibiae may be involved Often there is irregular but gross deformity of the pelvis and kyphosis of the spine with rarefaction and thinning of the vertebral bodies That the decalcification is quite general is indicated by the bending of the terminal phalanx of the thumb which is much used for pressure in many occupations

Fractures are frequent and in advanced cases contribute greatly to the picture of bizarre deformities Although the decalcified bones are broken with great ease they offer no special difficulties in healing, the callus usually being of normal character

Muscular Weakness — In hyperparathyroidism there is diminished excitability of nerves and muscles a condition apparently the exact opposite to that of tetany The muscles may be moved but are unusually flabby Weakness is a constant complaint and may be so extreme as to cause semi invalidism or even to prevent walking The deep reflexes are not abolished and indeed in some patients are exaggerated Electrical tests show diminished response to stimula

tion[73] In one of the cases described by Barr and Bulger (Fig 3) the muscular weakness was combined with an abnormal mobility of joints

Genitourinary Symptoms — Complaints referable to the urinary tract may be the first to call attention to the disease Albright[18] has emphasized that these may be dependent upon three types of lesion (1) pyelonephritis secondary to the formation of calcium phosphate stones (2) nephrocalcinosis in which calcium deposits in renal parenchyma are predominant (3) acute parathyroid poisoning with calcium deposits in the kidneys as well as in other organs The symptoms associated with the formation and development of stones in the pelves or ureters are the same as those from nephrolithiasis of any origin Due to irritation or infection of the bladder frequency of urination may be an early symptom Polyuria may occur even in patients whose renal function otherwise appears to be normal It may be so marked as to suggest diabetes insipidus There may be intermittent attacks of pain Renal insufficiency may occur from hydronephrosis or from pyelonephritis in association with stones or from extensive renal calcinosis

Circulatory Symptoms — Cardiac irregularities and conduction defects have been noted[56] High blood pressure may or may not accompany the renal insufficiency of the disease[135, 137]

Hematological Manifestations — Because of extensive fibrosis of the bone marrow anemia and leucopenia have been encountered occasionally in hyperparathyroidism Increased viscosity of the blood which is seen when excessive amounts of parathormone are given experimentally is not often a feature of clinical cases

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which is to be expected in all cases except those which have developed a complicating renal insufficiency[137, 52] The calcium content of the serum usually is increased In a review of 114 cases of hyperparathyroidism, in which the calcium concentration of serum was recorded, Gutman[2] found that 109 had over 11 mgm and 91 had over 12 mgm per 100 c c Albright and his associates[1], however reported a number of proven cases of hyperparathyroidism, in which the average concentration of the serum was below 12 mgm per 100 c c In a case observed by Snapper[130] calcium in the serum reached the quite astounding value of 23 6 mgm per 100 c c Inorganic phosphorus usually is diminished Of 79 cases in Gutman s series values of less than 2 5 mgm per 100 c c were recorded in 35 In some the serum phosphorus has a value of less than 1 5 mgm per 100 c c In cases with renal damage or on occasions when the calcium values are greater than 15 mgm per 100 c c the inorganic phosphorus may be normal or rise above normal levels During active stages of the disease alkaline phosphatase is increased above normal indicating perhaps a marked tendency to bone repair in a disease in which osteoclastic processes are predominant In one case a high level of acid phosphatase was recorded[56]

Diagnosis

In considering the diagnosis of hyperparathyroidism the experience of the group at the Massachusetts General Hospital is instructive Of 67 cases reported by Cope[48] 30 per cent were diagnosed because of osseous tumors and cysts 15 per cent because of decalcification of the skeleton and renal stones, while 55 per cent were recognized because of renal stones alone Obviously the condition must be suspected in all diseases of the skeleton and in all cases showing evidence of renal stones Other symptoms, which may suggest the diagnosis are weakness diminished tone and lessened excitability of muscles Tumors or cysts of the jaw or even malposition of teeth may call attention of the alert dentist to the possibility of the disease Confirmation usually will depend upon the demonstration of hypercalcemia or of abnormal excretion of calcium in the urine The Sulkowitch test and its modifications have proved useful in early diagnosis

Hypercalcemia is rare in conditions other than hyperparathyroidism An increase of serum calcium has been seen after the administration of large amounts of viosterol and has been shown by Brown and Roth[36] in patients suffering from polycythemia Although it has been reported in some cases of gout and arthritis most observers have failed to demonstrate it It may appear dissociated from parathyroid overactivity in conditions in which serum protein is greatly increased, and it is necessary as McLean and Hastings[107] have shown to take protein into account in evaluating serum calcium levels The presence of hypercalcemia always should suggest hyperparathyroidism and if the previously mentioned conditions can be excluded may be regarded as pathognomonic

The importance of early diagnosis has led to attempts at inclusion under the category of hyperparathyroidism many conditions which have no relation to it. It is not surprising that confusion has arisen concerning the generalized demineralization of the skeleton which is encountered so frequently in post menopausal women, in eunuchoidism, in Cushing's syndrome and in old age. It is now clear that these rarefactions of the skeleton are due primarily not to a process of decalcification but to a failure in the formation of the normal matrix of the bone in which calcium is deposited.

From the standpoint of the roentgenologist there may be also some confusion of diagnosis with adult rickets or osteomalacia. While the pictures in these conditions may be quite similar, the mechanism is different in that the defect arises from a failure in depositing calcium rather than from an increased tendency to decalcification.

A few years ago an attempt was made to show that Paget's disease (osteitis fibrosa) was a form of hyperparathyroidism. Essential differences in pathology as well as the failure to demonstrate hypercalcemia or parathyroid hyperplasia in Paget's disease have served to exclude the possibility.

Of great interest in the differential diagnosis are the cases collected and described by Albright[6,21] and variously designated as Albright's disease, osteitis fibrosa cystica disseminata, fibrous dysplasia of bone and polyosteiotic fibrous dysplasia. This condition is characterized by brown spots (cafe au lait spots) on the body, soft tissue tumors (neurofibromata), occasional precocious puberty in females and involvement of any part of the skeleton, often unilateral but never generalized. An excellent review of this desease has been published recently by Thannhauser[137] who regards it as a form of neurofibromatosis, an interpretation more recently questioned by Jaffe. It is not associated with any demonstrable changes in calcium metabolism.

In considering the differential diagnosis account must be taken also of conditions which produce secondary hyperparathyroidism. Occasionally there may be difficulty in differentiating renal insufficiency which has arisen because of hyperparathyroidism from renal difficulty which is primary and has led to overactivity of the parathyroids.

In the literature there are cases which have been diagnosed as renal calcinosis or renal rickets but which on review seem to be classified better as primary hyperparathyroidism. Some confusion may arise also between osteitis fibrosa cystica and multiple myeloma or carcinomatous metastases to bone especially when such cases are accompanied by hyperplasia of the parathyroid glands, by hypercalcemia, hyperphosphatemia and generalized decalcification of the skeleton. At times diagnosis must rest on the radiological appearance of the osseous lesions or upon the historical evidence that they have developed from a primary tumor.

Treatment

Medical treatment in hyperparathyroidism is of little or no avail While demineralization and to some extent, the fibrocystic disease of bone may be prevented by the intake of large amounts of calcium and phosphorus, this treatment in itself predisposes to the even more serious nephrolithiasis and nephrocalcinosis Irradiation of the parathyroid glands in cases of tumor or hyperplasia has not been encouraging although individual cases have appeared to respond with temporary benefit

The treatment of choice is surgical, but there is general agreement that for the best results special experience in parathyroid surgery is desirable or at times essential[41 46 47 48] Even a surgeon of great experience may have difficulty in locating the glands or in correctly identifying a tumor The parathyroids may number as many as twelve, they may be scattered in the substance of the thyroid gland in the thymus or in the anterior or posterior mediastinum Furthermore, there may be considerable difficulty in differentiating parathyroid from thyroid tissue or even from globules of fat In some cases the tumor has been found only after two or more explorations For more complete examination in difficult cases Cope has devised a two stage operation in which the neck and posterior mediastinum are explored first with a later exploration of the anterior mediastinum and the region of the thymus gland

There is considerable danger of tetany following the removal of a tumor or of a large amount of hyperplastic tissue Symptoms may develop in a few hours and, unless promptly and thoroughly treated may be rapidly fatal The likelihood of such an occurrence to some extent is predictable by a study of the level of alkaline phosphatase which tends to be high in cases showing intense osteoblastic activity and hence a tendency to rapid withdrawal of calcium from the circulation Treatment with calcium gluconate parathormone and calciferol should be prompt and is conducted as in other cases of acute tetany as described earlier in this chapter

To avoid such emergencies probably it is wise to administer prophylactically 100 000 to 400 000 units of calciferol with 6 to 12 grams of calcium lactate or calcium gluconate each day from the day of operation until all danger of tetany is passed The use of the Sulkowitch test at frequent intervals is of much assistance in anticipating the onset of tetany and in judging safe dosage of calciferol and calcium Complete absence of a precipitate in the urine indicates a serum calcium of 8 mgm per 100 c c or lower and a heavy precipitate indicates undesirably high calcium levels

Results of surgical treatment often are brilliant However, a follow up of every patient for a number of years should be carried out routinely Examination of the urine by the Sulkowitch reagent should disclose undesirable levels of cal

cium in the serum X rays of the skeleton taken at three month intervals will reveal remineralization in favorable cases If the disease has been associated with nephrolithiasis or with renal calcinosis the removal of a tumor or hyperplastic tissue may do no more than prevent further deposits Renal insufficiency if apparent before operation may remain uncorrected Danger of secondary urinary tract infection is considerable Deaths from renal infection and failure in cases otherwise aided have not been infrequent

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CHAPTER XV-A

DISEASES OF THE THYROID GLAND

By Samuel L. Gargill and Mark Falcon Lesses

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PART I

ANATOMY BIOCHEMISTRY AND PHYSIOLOGY OF THE THYROID

Anatomy

In man the thyroid gland originates during the third week of embryonic life as an invagination of the pharyngeal entoderm anterior to the tracheal invagination In later life the site of its origin is the foramen cecum located at the base of the tongue At first a hollow tube the *thyroid anlage becomes a solid mass of cells which later descend through* the thyroglossal tract into the anterior portion of the neck forming epithelial bands and fenestrated plates The primary thyroid follicles arise directly *from these epithelial plates* The *thyroglossal tract* usually disappears early in embryonic life Thus embryologically the thyroid gland is a detached clump of entodermal tubules in front of the trachea [1]

The human thyroid attains full size just before puberty The gland normally comprises two lateral lobes connected by an isthmus An additional lobe known as the pyramidal lobe may be present especially in areas of endemic goiter This lobe arises from epithelial rests along the thyroglossal tract and is recognizable as a strip of tissue reaching from the isthmus toward the hyoid bone on the left side of the thyroid cartilage The adult thyroid normally weighs between 20 and 25 gm averaging *0 4 gm per kilo of body weight it is larger in women than in men* The whole gland is firmly attached to the trachea and therefore moves with that organ in swallowing

The blood supply of the thyroid gland is of such magnitude that it clears the total blood volume of a normal man in about one hour The blood is delivered to the gland through the four thyroid arteries the right and left superior and inferior arteries The superior descend from the external carotid artery to the upper poles of the thyroid The inferior arise from the subclavian arteries to reach the posterior surface of the lower poles Occasionally the median thyroidea ima artery is encountered *ascending from the innominate artery in front of the trachea to*

into the deep cervical retrosternal tracheal and anterior laryngeal lymph nodes

Both sympathetic and parasympathetic fibers innervate the thyroid gland The sympathetic fibers are derived from the second to the fifth thoracic segments passing through the superior and middle cervical ganglia, whence they are relayed to the gland through the superior laryngeal nerve and along blood vessels The parasympathetic fibers are derived from the vagus and enter the thyroid by way of the superior laryngeal nerve The exact role of the rich innervation of the thyroid is as yet undetermined, it is clear that there is a complex and sensitive vasomotor control but it is uncertain whether nervous control of hormonal secretion exists



Fig 2 Cross section of normal human thyroid Cross section of the superior anterior region of the dissected left lobe shown in Fig 1 demonstrates anastomosing channels or spaces forming a fenestrated labyrinth It is to be noted that clefts do not completely traverse the gland From Rienhoff W F Jr Arch Surg 1929 xix 986 1036

The parenchyma of the thyroid has been shown by Rienhoff to be a complex mass of tissue irregularly subdivided into many areas These areas of tissue consist of groups of follicles of varying number size and shape The parenchyma itself is unevenly compartmented by connective tissue septa which convey the blood vessels nerves and lymphatics (Figs 1 and 2)

the lower portion of the thyroid gland These larger arteries divide and ramify over the surface of the gland, whence penetrating vessels enter deeply into the thyroid structure forming a capillary bed around each follicle

The venous drainage starts from the perifollicular plexus and empties into the internal jugular veins by way of the superior and middle thyroid veins and into the innominate veins by way of the inferior thyroid veins Lymphatic drainage is provided by a perifollicular plexus which empties

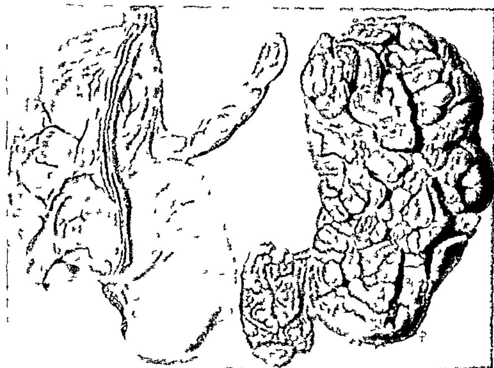


Fig 1 Normal human thyroid right and left lobes together with the isthmus The dotted line shows where the isthmus which in the section was left attached to the left lobe joins the base of the right lobe The right lobe is shown covered with fascia as it was found in the cadaver The anterior branch of the superior thyroid vessels is seen descending from the upper toward the lower pole From the junction of the upper portion of the right lobe can be seen a bizarre pyramidal lobe The isthmus and the left lobe are shown with all fibrous tissue investment including blood vessels nerves and lymphatics dissected away It is to be noted that there are no true lobules but a complex mass of parenchyma irregularly divided by an intricate anastomosing system of spaces or channels forming within the gland a veritable fenestrated labyrinth The gland as shown is made up of regions of connecting bars bands or plate like regions composed of individual discrete follicles or acini The stippled appearance of the surface represents the follicles From Rienhoff W F Jr Arch Surg 1929 xix 986 1036

into the deep cervical retrosternal tracheal and anterior laryngeal lymph nodes

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The follicle is the structural and functional unit of the thyroid It is a cyst-like structure varying in size from 50 to 1000 mu with an average measurement of about 300 mu A single layer of simple epithelial cells, low columnar or cuboidal comprise the wall of the follicle, within which there is a varying amount of a hyaline uniform material called colloid' The follicles vary in shape from a sphere to a cube, thus many are rounded while others are angular Each follicle is an isolated unit, and evidence is lacking for any intercommunication (*Fig* 3)

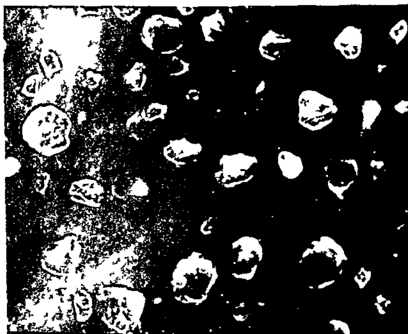


Fig 3 Group of follicles dissected from normal human thyroid Spherical shape together with the variability and thickness of the epithelial mass as evidenced by the difference in the photographic shadow cast is well brought out From Rienhoff W F, Jr Arch Surg 1929 xix 986 1036

The thyroid cell is a complex structure containing a large rounded reticular nucleus and cytoplasm in which special stains have demonstrated mitochondria and the Golgi apparatus The former are granules or filaments whose structure parallels quantitatively the secretory activity of the gland [3, 4] The Golgi apparatus is a coarse thread like structure of the cytoplasm which occurs in the thyroid gland as well as in other secretory glands such as the pancreas and ovaries Its form and position vary with the activity of the cell and eventually it becomes fragmented

Cramer and Ludford[3] have advanced the interesting theory that the mitochondrial granules serve to increase or decrease the intracellular surfaces in accordance with secretory requirements Ingram[5] showed that the size of the Golgi apparatus is proportional to the size and secretory content of the follicular cells The height of the cell itself is a useful index of thyroid function for the cell elongates with increased activity and becomes flattened with rest[6]

The manner in which the thyroid cell secretes its hormonal produce has been demonstrated by Williams[7] who observed living thyroid follicles implanted in the ear of the rabbit The follicles underwent cyclic changes in activity divisible into these four stages (1) secretion characterized by an increasing refractility of the thickened walls and by the roundness of both follicle and colloid (2) secretion and colloid release characterized by further increase in refractility of the walls with diminution in their thickness increase in colloid and in active follicles by irregularity of the internal border of the wall the irregularity being explained tentatively as due partly to compression of exhausted cells to such a degree that diffusion of colloid across them can take place this appears to be the chief mechanism of colloid release (3) partial collapse caused by colloid release at greater velocity than colloid production (4) recuperation characterized by an opacity of the walls which are thickened and enclose very little colloid Williams concluded that secretion is toward and into the lumen by diffusion

The nervous innervation of the follicle appeared to play no part in secretion under the conditions of his experiment On the other hand anterior pituitary extracts containing the thyrotrophic hormone augmented colloid production and release

The mechanism of release of follicular colloid in man has been considerably elucidated in studies on necturus by Grant[8] who demonstrated that stored colloid emptied into the blood capillaries surrounding the follicles under the influence of anterior pituitary implantation As a consequence of her experiments she has advanced a theory of transcellular colloid release During the transfer stage the colloid in the follicle cells is seen first as large refractile droplets which later appear fine and emulsified Since the follicles showed progressive emptying the colloid content of the cells must be regarded as proof of transcellular colloid release rather than as a product of synthesis The mechanism by which the colloid crosses the cell boundary is unknown though emulsification enzymatic digestion and phagocytosis have been variously advanced as possible explanations In the mammalian gland the follicular cells per

haps transport the colloid through their cytoplasm in an unstainable form, in necturus one can obtain histological proof of this method of colloid export

Gersh and Caspersson,[9] through studies of frozen-dried thyroid gland sections with the ultraviolet microscope, have contributed significantly to the understanding of colloid release Thyroglobulin has a characteristic absorption curve in the ultraviolet region of the spectrum, with absorption characteristics allowing separation of tyrosine and tryptophane on the one hand and thyroxine and diiodotyrosine on the other Application of this knowledge through methods developed by Caspersson allowed the quantitative concentration of total protein in the colloid and of thyroxine and diiodotyrosine in both colloid and cells to be determined The protein-bound iodine comprising thyroxine and diiodotyrosine, was found homogeneously distributed in the colloid The administration of potassium iodide or anterior pituitary extract produced continual secretion of colloid into the lumen for storage and subsequent reabsorption Markedly stimulated glands showed secretion directly toward the blood vessels

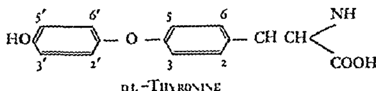
Dempsey[10] has also investigated the histochemistry of the thyroid through a study of its fluorescent qualities Intrafollicular colloid the follicular cells connective tissue and thyroid pigment revealed autofluorescence when viewed through an ordinary microscope illuminated with ultraviolet rays Deficient fluorescence of the colloid occurred in iodine and hormone-deficient glands Further studies of the chemical cytology of the thyroid by Dempsey and Singer[11] have provided evidence that the colloid contains a conjugated protein ribonucleoprotein, in addition to the simple protein thyroglobulin The significance of this finding in relation to thyroid physiology is at present unclear These authors and others have found both alkaline and acid phosphatases in the thyroid gland apparently participating in its intermediary carbohydrate metabolism The phosphatases are deposited in varying concentration in some of the endothelial cells of the capillaries thus suggesting a mechanism for controlling migration of metabolites through the capillary wall (Plates 1 and 2)

Biochemistry

The epithelial cells of the follicle secrete the colloid substance, which is stored within the lumen The thyroid hormone is ordinarily contained

in this material and thus it represents a unique example of an internal secretion that can be visualized with the microscope Thyroglobulin can be extracted from the gland with physiological salt solution and by appropriate precipitation with varying concentrations of ammonium sulfate its proteins may be salted out [12] Bauman [13] in 1896 first showed that the thyroid protein contained iodine and that the iodine in the gland was organically bound Hutchison [14 15] recognized that the protein was globulin and later investigation has demonstrated that except for its iodine content this iodo thyroglobulin does not differ markedly from *other globulins of animal origin* [16] *The molecular weight of thyroglo*bulin has been determined to be about 675 000 [17]

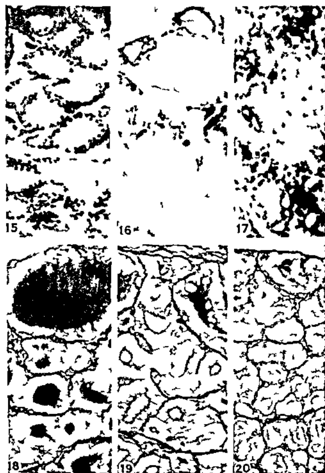
The iodine of the thyroid is derived immediately from the circulating blood and ultimately from the iodides and iodates of ingested food and water Iodates are converted to iodides in the intestinal tract and are absorbed in the latter form By means of radioactive iodine [18] it has been established that the thyroid of the normal rabbit is saturated with the halogen within 15 minutes after an intravenous iodine injection The iodine thus acquired is organically bound for hormone synthesis or rediffuses into the blood stream The normal thyroid gland does however contain 7 per cent of its total iodine in inorganic form



DL-THYRONINE

The physiological potency of thyroglobulin depends chiefly upon its content of two iodine-containing amino acids namely thyroxine and diiodotyrosine the former probably accounting for 29 per cent and the latter for 64 per cent of the total iodine in the normal gland Thyroxine containing 65 per cent iodine was isolated by Kendall in 1915 [19] Harington [0] proved that thyroxine is an amino acid with four iodine atoms a hydroxyphenyl ether of tyrosine or 3 5 3 5 tetra iodothyronine Harington and Barger [21] later synthesized thyroxine by conjugating two molecules of diiodotyrosine

Plate 1



15 Fructose diphosphatase reaction pH 9 5 in the endothelial and follicular cells of the thyroid gland from a normal control rat The section was incubated for 24 hours in the substrate mixture and the precipitated phosphate was visualized by trans formation to cobaltous sulfide Fixation in cold 80 per cent alcohol

16 *Thyroid gland from a rat exposed to cold illustrating the reduction in the alkaline* fructose diphosphatase reaction The enzyme does not appear in the endothelium or parenchymal cells associated with the central or most active follicles, but is restricted to the peripheral inactive portions of the gland Fixation in cold 80 per cent alcohol

17 Alkaline fructose diphosphatase in the thyroid gland of a rat to which thiouracil had been administered Fixation in cold 80 per cent alcohol

18 Argyrophilia of the colloid from the thyroid gland of a normal control rat Bouin fixation, section digested in saliva Pap s stain

19 Section illustrating the reduction in argyrophilia particularly in the central fol licles from a rat exposed to cold Bouin fixation section digested in saliva Pap s stain

20 Section illustrating the further reduction in argyrophilia in the thyroid gland of a rat to which thiouracil had been administered Bouin fixation Sections digested in saliva, Pap s stain

From Dempsey W W and Singer M Endocrinology 1946 xxxviii 270-95

Plate 2



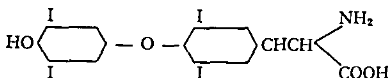
21 Drawing illustrating the localization of alkaline glycerophosphatase (pH 9.4) in the follicular cells of peripheral follicles from the thyroid gland of a normal control rat The endothelial cells are negative Fixation in cold 80 per cent alcohol Section incubated in substrate mixture for 6 hours

22 Drawing illustrating the localization of acid glycerophosphatase in the nuclei and parenchymal cells of the central follicles from the thyroid gland of a rat exposed to cold Fixation in 80 per cent alcohol Section incubated 48 hours

23 Drawing illustrating the argyophilic granules of the follicular epithelium of a normal control rat This appearance has been observed only after Zenker fixation

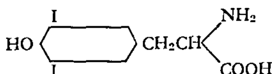
24 Argyrophilic granules in the thyroid gland from a rat after exposure to cold Zenker Fixation Pap s stain

From Dempsey W W and Singer M Endocrinology 1946 xxxviii 270–95



THYROXINE

This compound has been isolated in pure form from the gland by Oswald in 1911 and from the colloid by Harington and Randall in 1929.[3] Diiodotyrosine has the following structural formula:



The biosynthesis of thyroxine appears to involve two stages: first, the iodination of tyrosine; second, the coupling of two molecules of diiodotyrosine to form thyroxine. The derivation of diiodotyrosine from the essential amino acid tyrosine has been established by various methods. It probably involves oxidative processes capable of liberating iodine from iodide to make it available for attachment to the tyrosine molecule. Cavett[4] analyzed various thyroglobulins with regard to their amino acid content and found the tyrosine content to vary inversely with the content of thyroxine and diiodotyrosine. He also showed that thyroglobulins low in iodine had a greater content of tyrosine and conversely that thyroglobulin from the glands of patients treated with iodine had more diiodotyrosine and thyroxine and less tyrosine. This ability of the thyroglobulin molecule to alter its composition of amino acids explains the mechanism whereby iodine content and physiological potency of thyroglobulin may be varied.

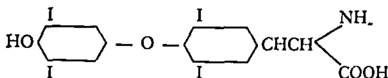
Further proof that iodination of tyrosine is the first step in the synthesis of thyroxine has been furnished through the use of radioactive iodine as a tracer substance. This has been utilized by injecting radio-iodine into animals and determining the subsequent distribution of radioactivity in the body, or by studying the respiration of thyroid tissue slices in a medium to which radioactive iodine had been added and whose fate could be traced. Following the injection of radio-iodine into animals there is rapid concentration of iodine in the thyroid gland.[6, 7] This occurs quickly, within a matter of minutes, and proceeds until as

much as 50 per cent of the radioactive material is found in the thyroid *gland after 48 hours. With tracer doses Morton and his co-workers*[29] have repeatedly shown that almost all of the radio-iodine deposited in the gland is organically bound within one hour. The radioactive iodine is distributed among three fractions: inorganic iodide, diiodotyrosine and thyroxine. With passage of time there is gradual increase in the amounts of diiodotyrosine and thyroxine and decreasing amounts of inorganic iodide. This work, combined with the studies of Cavett mentioned above, shows clearly the reciprocal relationship existing among tyrosine, inorganic iodide, diiodotyrosine and thyroxine.

When large amounts of radioactive iodine are added to the medium in which surviving thyroid tissue slices are respiring, there is rapid incorporation of the radio-iodine in the tissue. As in the in vivo experiments, the radioactivity is associated at first with diiodotyrosine and later appears *with thyroxine, thus indicating a process of conversion similar to that* seen in the intact animal.[8, 31] It is of interest, however, that Schachner, Franklin and Chaikoff[21] demonstrated that surviving thyroid slices were able to concentrate up to 60 per cent of added radio-iodine even after the inhibition of thyroxine and diiodotyrosine formation by azide or sulfanilamide. Cyanide and sulfide, in addition to inhibiting thyroxine and diiodotyrosine formation, also blocked the accumulation of radio-iodine by thyroid slices. From this selective blocking of iodine concentration and thyroxine formation these authors concluded that thyroid tissue possesses an additional mechanism for concentrating iodine that does not depend upon conversion of inorganic iodide to thyroxine and diiodotyrosine.

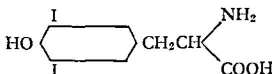
The role of tyrosine in the synthesis of thyroxine and as a scaffold for the attachment of iodine to the protein molecule may be best appreciated by Harington's statement[32] that "it is possible by choosing the proper conditions almost to titrate the tyrosine in a protein with iodine." While thyroxine and diiodotyrosine are the major iodine-containing compounds of the thyroid, chromatography has demonstrated that others are present, particularly monoiodotyrosine,[4, 38] in amounts up to 15 per cent of the total iodine.

Iodination of tyrosine is the first step in hormone synthesis. The coupling of diiodotyrosine to form thyroxine as the final step in the process must be considered in relation to certain enzyme systems that are involved in intracellular respiration. Oxidation within the cell requires enzymatic action because the usual metabolites of the body are not autooxidizable. There are cellular iron-containing pigments known as cyto-



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cytochrome C cytochrome oxidase system using an enzyme preparation from the rat heart

Thyroglobulin thus appears as a complex protein which incorporates three iodine containing amino acids in its molecule through iodination of tyrosine The iodine content of the normal human thyroid varies from 0 05 to 0 45 per cent of the dry gland [43] or from 0 5 to 4 5 mg per gram of dried thyroid The average iodine content of dried glands throughout the world is close to 0 2 per cent [44] (2 mg per gram dried gland) The iodine content varies depending upon the activity of the gland season of the year geography and food habits [45 46 47]

While the thyroid gland selectively fixes about 20 per cent of the body s iodine organically bound iodine is present in other tissues and thyroxine like fractions have been biologically demonstrated in these tissues The role of this extrathyroidal organic iodine is not clear but is undoubtedly significant

Chapman [48] found that the level of iodine intake had a pronounced effect on the weight surface area metabolic rate and food utilization of thyroidectomized animals those with higher iodine ingestion showing an effect which suggested that iodine might play a role in production of a thyroxine like substance in the tissues This aspect of extrathyroidal hormone production was more definitely established by Morton Chaikoff and their collaborators [49] through the use of radioactive iodine From 2 to 8 months following thyroidectomy radio-iodine was injected into young rats who were then killed at intervals of 2 to 96 hours after the injection Measurable quantities of labeled thyroxine and diiodotyrosine were found in the liver muscles and small intestines The completeness of the thyroidectomy was checked both by serial section and by the radio autographic technique

These experiments indicate that tissues other than the thyroid possess the ability to elaborate small amounts of a thyroid like substance Harington [39] explains the extrathyroidal synthesis of thyroxine as a general biological function of almost any living tissue containing adequate amounts of iodide since tissue proteins will contain tyrosine bound in a peptide linkage whence it can undergo the reactions leading to thyroxine This would leave the thyroid gland the specific functions of concentrating iodine in large amounts of increasing the rate of formation of thyroxine and of storage of iodine containing amino acids in the form of thyroglobulin The possibility of this extrathyroidal synthesis of thyroxine is not surprising in view of studies on artificial iodo-proteins. Oswald [2] isolated crystalline diiodotyrosine from hydrolysates of iodi

chrome a b, and c, which are widely distributed in aerobic cells of many kinds and are especially abundant in tissues with large oxygen consumption Oxidation of these pigments by molecular oxygen is accomplished by a respiratory enzyme known as cytochrome-oxidase This enzyme which is readily inhibited by cyanide, is especially important in the oxidation of cytochrome a and c, less so for b, which is to some extent self-oxidizing[35] With the aid of radio iodine Schachner Franklin, and Chaikoff[36] have demonstrated that the formation of both diiodotyrosine and thyroxine in the thyroid is accomplished through intracellular aerobic oxidations involving the cytochrome-oxidase system The need for cellular organization was indicated by the fact that homogenized thyroid tissue had lost its capacity to incorporate radio iodine This incorporation does not occur with complete anerobiosis Furthermore, typical inhibitors of cytochrome-oxidase such as cyanide, azide, sulfide, or carbon monoxide, block the formation of diiodotyrosine and thyroxine from inorganic iodide in thyroid slices Dempsey[10] has found cytochrome-oxidase in the cells of the thyroid follicle and has also presented evidence for the presence of peroxidase in the thyroid cells The peroxidase reaction was easily inhibited by thiouracil, whereas the cytochrome-oxidase reaction was unaffected DeRobertis and Grasso[37] have confirmed these findings

Harington[38, 39] has postulated that the enzymic oxidizing system liberates iodine from iodides and that this free iodine is the effective oxidizing agent which converts both tyrosine to monoiodotyrosine and diiodotyrosine and the latter to thyroxine According to Harington[39] diiodotyrosine or its derivatives in alkaline solution speedily liberate small amounts of iodine so that it is readily available as an oxidizing agent Mild reducing agents that react with iodine, such as thiosulfate and many antithyroid drugs inhibit this reaction Further support to this view has been lent by Keston[40] who found that iodine and oxidases participate in the reaction which organically binds iodine Recently Reineke and Turner[41] after a study of the factors influencing the iodination of casein, concluded that manganese had an important catalytic role in the promotion in vivo of thyroxine formation Ray and Deysach[42] had earlier shown the particular ability of the thyroid to store manganese

Thyroxine itself has an important role in enzymatic mechanisms Gemmill[43] demonstrated that thyroxine increases the rate of oxidation of the ascorbic acid ascorbic acid oxidase system (plant origin) and inhibits the cupric ion catalyzed oxidation of ascorbic acid Thyroxine was also found to stimulate the oxidation of succinate in the dehydrogenase-

Harington has demonstrated that naturally occurring thyroxine is 3 5 3 5′ tetraiodo L thyronine The non halogenated amino acid DL-thyronine which resembles thyroxine structurally lacks thyroxine like activity The addition of iodine in the 3 and 5 positions to thyronine produces some thyromimetic action at a level of 1/15 to 1/40 of that of DL thyroxine If other halogens namely chlorine bromine and fluorine are added to thyronine thyroxine like activity develops but none is so potent as iodine Harington has concluded that thyromimetic activity develops only when the halogen atoms are present in the 3 and 5 positions of the thyronine nucleus Lerman Harington and Means [58] have found that the substitution of bromine or chlorine for iodine diminishes considerably the activity of the thyroxine molecule Tetrabromthyronine has 3 per cent and tetrachlorthyronine has 0 . per cent of the activity of L thyroxine

Naturally occurring thyroxine is levorotatory Commercially available thyroxine has usually been racemic (that is DL thyroxine) because it has been easier to isolate and synthesize in this form L thyroxine however, is now commercially available and has been found by us to be effective in the trea ment of myxedema The L isomer is much more potent than D thyroxine according to Gaddum ' Reineke and Turner consider the activity of DL thyroxine to be due entirely to the presence of the L isomer

These biological mechanisms for incorporating iodine into the body chemistry present the unsolved question of why the organism has selected iodine from among the elements to aid in the formation of an important cellular stimulant The intimate relation of iodine to the sea suggests an ancient paleochemical origin of the hormone Chlorine another halogen had already been utilized to form an essential component of the marine environment of our ancestors as well as an abundant component of human blood The question cannot of course be answered but serves to focus attention on the chemical genealogy of the hormone

The Nature of the Circulating Hormone

While the nature of the circulating hormone is at present unclear it is established that it lies somewhere between the large moleculed protein thyroglobulin and the relatively simple iodine containing amino acid thyroxine if in fact it is not either thyroglobulin or thyroxine Thyroglobulin which appears to be the form in which the hormone is present

nated albumin casein and gliadin Ludwig and von Mutzenbecher [6] iodinated casein and other proteins, thus producing products whose physiological activity was shown to be due to contained thyroxine and from which thyroxine was actually isolated Harington and Pitt Rivers have confirmed this work [1] These artificial iodo proteins and various fractions of their hydrolysates have physiological effects similar to those of the thyroid hormone [3] The iodinated proteins are of more than theoretical interest as a source of thyroxine-containing protein Reineke and Turner [54] have successfully produced synthetic thyro proteins which have several times the thyroidal activity of U S P thyroid powder, as judged by assay on tadpoles or by yield of thyroxine This increased activity appears entirely explicable on the basis of a content of thyroxine more than three times that normally obtained in powders derived from the dried gland Of considerable interest in connection with this finding is the further fact that the iodination of protein yields maximal thyroidal activity with substitution of two atoms of iodine per molecule of tyrosine An increase in iodination beyond this yields products of lesser activity Co operative studies in England have shown that iodinated casein as well as other iodinated proteins serve as an adequate stimulant of milk yield in the cow in a manner exactly similar to dried thyroid gland and thyroxine Such proteins also maintain growth in young thyroidectomized rats and effect premature metamorphosis in tadpoles

Only two mechanisms are available to explain the formation of thyroxine which has been proved to follow the iodination of proteins (1) either the protein contained thyronine (this is thyroxine less all four of its iodine atoms) which directly added iodine to form thyroxine or (2) the iodine produced diiodotyrosine from tyrosine and was then converted into thyroxine The latter process is perhaps the more likely and has been demonstrated by von Mutzenbecher to occur in minimal amounts as mentioned previously Thus the synthesis of thyroid hormone in the body and the iodination of protein in the test tube appear to follow a similar chemical pattern

The chemical structure of thyroxine has been shown to be specific by Harington and McCartney [56] who found a chemical isomer of thyroxine lacking the thyronine configuration to be inert This has been confirmed and extended by other workers, who have shown that a high specificity of structure is required to produce significant activity Substitution of the iodine atoms in unusual places (e g at positions 4′, 6′) strikingly reduced activity [7] Niemann [8] has exhaustively reviewed the chemistry of thyroxine and related compounds

Harington has demonstrated that naturally occurring thyroxine is 3 5 3 5′ tetraiodo L thyronine The non halogenated amino acid DL-thyronine which resembles thyroxine structurally lacks thyroxine like activity The addition of iodine in the 3 and 5 positions to thyronine produces some thyromimetic action at a level of 1/15 to 1/40 of that of DL thyroxine If other halogens namely chlorine bromine and fluorine are added to thyronine thyroxine like activity develops but none is so potent as iodine Harington has concluded that thyromimetic activity develops only when the halogen atoms are present in the 3 and 5 positions of the thyronine nucleus Lerman Harington and Means[56] have found that the substitution of bromine or chlorine for iodine diminishes considerably the activity of the thyroxine molecule Tetrabromthyronine has 3 per cent and tetrachlorthyronine has 0 per cent of the activity of L thyroxine

Naturally occurring thyroxine is levorotatory Commercially available thyroxine has usually been racemic (that is DL thyroxine) because it has been easier to isolate and synthesize in this form L thyroxine however is now commercially available and has been found by us to be effective in the trea ment of myxedema The L isomer is much more potent than D-thyroxine according to Gaddum[9] Reineke and Turner consider the activity of DL thyroxine to be due entirely to the presence of the L isomer

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in the gland itself, has not been found as such in the circulating blood except in the thyroid veins during or immediately after thyroidectomy for toxic goiter Since Hektoen and his co-workers [61, 62] demonstrated that highly sensitive precipitin reactions to thyroglobulin could be developed through the use of immune serum the problem has been approached immunologically This earlier work was extended by Lerman [63] who was unable to demonstrate thyroglobulin in the serum of thyrotoxic or normal persons More direct evidence excluding thyroglobulin itself as the circulating hormone has been offered by Bassett, Coons, and Salter,[64] who found the major part of the circulating iodine in the albumin fraction, albeit the highest concentration of iodine was in the alpha and beta globulins

Harington [65] has presented immunological experiments which support his view that thyroxine is the effective form of the circulating hormone He immunized animals with artificial thyroxine-protein complexes, whose antigenic specificity was determined by thyroxine and diiodotyrosine groups The antibodies of the antiserum thus produced were specifically adapted to combine with the molecule of the physiologically active substance and thus were able to interfere with the action of this substance in another animal by a process analogous with passive immunization The antisera thus developed against the thyroxine protein complexes did not lower the metabolic rate of normal animals but did prevent the characteristic rise in metabolic rate caused by thyroglobulin or thyroxine This neutralization of the effect of thyroxine by the antisera showed that the circulating antibodies containing combining sites adapted to thyroxine interfered with the access of the latter to its normal sites of action in the tissues

Harington s hypothesis is only weakened by the work of Canzanelli and Rapport [66, 67] who found significant metabolic effects produced by thyroglobulin upon tissues in vitro and an absence of such effects by thyroxine Barker,[68] as well as Williams-Ashman,[69] however, have found no in vitro effectiveness of thyroglobulin

Craig and Salter [50] found that thyroxine when added to normal blood did not induce the calorigenic action in excised surviving tissues that was readily produced by the blood of thyroxinized animals, thus suggesting that thyroxine is altered in some way before becoming the effective form of the hormone Thyroxine however has been found a complete metabolic substitute for the functioning thyroid gland in the living organism

Gross and his associates [70] found that thyroxine, after its release by the thyroid gland circulates in combination with plasma proteins This

combination may be readily separated by butanol but is reconstituted when thyroxine is placed in contact with plasma proteins In further attempts to identify iodine compounds other than thyroxine and iodide in human plasma Gross and Pitt Rivers [70b, 70c] succeeded in demonstrating the presence of an iodine-containing substance in the plasma of patients given radioactive iodine which behaved in a manner identical with that of 3 5 3′ L triiodothyronine on two dimensional paper chromatograms and on a kieselguhr column They concluded that this substance triiodothyronine is a normal constituent of the organic iodide fraction of plasma since they found it in the plasmas of both euthyroid and hyperthyroid individuals The steps in the biological synthesis of thyroid hormone they formulated as follows (1) oxidation of iodide to iodine (2) iodination of tyrosine to diiodotyrosine (3) coupling of molecules of diiodotyrosine to give 1 molecule of thyroxine and (4) deiodination of thyroxine to give triiodothyronine

Triiodothyronine was then assayed in thiouracil treated rats by its effect in preventing goiter [70d] The activity of triiodothyronine was found to be about three times that of L thyroxine and it was concluded that triiodothyronine is probably the form of the thyroid hormone that is active in the tissues Its effect in myxedema was then studied [70e] by administering it to two hypothyroid patients in a daily dose of 80 micrograms This dose had an effect similar to that of a daily oral dose of 100 to 300 micrograms of L thyroxine the basal metabolic rate and blood cholesterol levels returned to normal and at the same time the patients lost weight during the treatment

The metabolic effects of triiodothyronine as well as the metabolism and distribution of radioactive triiodothyronine have been further studied Asper and his co-workers [70f] observed that triiodothyronine produced an immediate metabolic effect five to ten times that of equivalent doses of L thyroxine in patients with myxedema Within six hours after its administration in a single subcutaneous dose (0 5 to 1 0 mg) progressive increases in pulse rate and body temperature occurred reaching a maximum on the third day The basal metabolic rate increased promptly and there was acceleration of urinary creatine excretion as well as nitrogen and phosphorus diuresis with resultant negative nitrogen and phosphorus balances and weight loss The serum protein bound iodine levels increased after administration of triiodothyronine although they frequently remained in the hypothyroid range when the patients were metabolically euthyroid L thyroxine on the other hand increased the PBI values to euthyroid levels although the

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the enterohepatic circulation Both substances rapidly disappeared from the body after 15 days 1.5 per cent of triiodothyronine and 2.5 per cent of thyroxine radioactivity remained After injection of triiodothyronine 54.8 per cent of excreted I^{131} appeared in the urine compared with 36 per cent after injection of thyroxine Thyroxine was selectively retained in the liver so that after 15 days more than 55 per cent of residual radioactivity was in the liver and less than 40 per cent in the carcass Fifteen days after triiodothyronine injection virtually all radioactivity was either in the thyroid or in the carcass This again suggests that triiodothyronine may be the active form of the hormone in the tissues

If the circulating hormone is thyroxine or some other hydrolytic product of thyroglobulin there should exist an enzyme system in the gland itself capable of breaking down thyroglobulin by proteolysis into smaller components which can cross cell membranes The existence of such an enzyme system has been demonstrated and its activities quantitated by DeRobertis and Nowinski [1] who measured proteolytic activity by determining the formation of tyrosine and tryptophane from the protein edestin through the action of excised human thyroid glands They found approximately a 100 per cent increase in proteolytic activity in the thyrotoxic gland as compared with the normal and about a 25 per cent decrease in iodized thyrotoxic glands and in non toxic diffuse goiters

PHYSIOLOGY

If thyroglobulin is essentially the storage form of the thyroid hormone then one would expect thyroxine to be the amino acid to which it owes all of its activity The results of physiological assays have proved con tradictory, however While thyroxine completely relieves human myx edema it has been claimed that desiccated thyroid or thyroglobulin produces a calorigenic effect greater than can be accounted for by their thyroxine content Thus Reid Hunt [7] showed by means of the acetonitril test that desiccated thyroid produced an effect greater than the equivalent amount of thyroxine (as iodine) in protecting mice against cyanide poisoning This presumed superior effectiveness of thyro globulin and desiccated thyroid cannot be due to a simple summation of the activity of diiodotyrosine and thyroxine because the former by itself has but little calorigenic effect [3, 4] Moreover 3 5 diiodothyronine (thyroxine less two of its iodine atoms) has but 4 per cent of the activity

patients were still hypothyroid Serum cholesterol levels decreased following the administration of either compound, but the decrement bore no quantitative relationship to the degree of metabolic change Electrocardiograms reverted more rapidly to normal after triiodothyronine than after L-thyroxine therapy

The paradoxical effect of triiodothyronine on the serum protein bound iodine was also noted by Starr and Liebhold Schneck,[0g] who found that sodium levothyroxine in a dosage of 0 075 mg, orally, usually reduced radioactive iodine uptake by the thyroid of normal human subjects and that this was associated with a rise of protein bound iodine when a dosage of 0 2 mg or more was given, whereas triiodothyronine in a dosage as low as 0 008 mg orally also reduced the uptake but was associated with a decrease in serum protein bound iodine

Blackburn and his associates[70h] compared the calorigenic effects of triiodothyronine and thyroxine given intravenously to myxedematous patients The initial response to triiodothyronine appeared sooner and reached a maximum in 24 to 48 hours whereas the maximal response to thyroxine occurred in 7 to 10 days The biologic decay rate of the two substances was found to be similar and possibly identical, and therefore Blackburn and his co-workers concluded that the total calorigenic effects were substantially the same Wiswell and Asper[01] found that triiodothyronine like thyroxine was not effective in stimulating oxygen consumption when added directly to intact tissues incubated in vitro but was more potent than thyroxine in accelerating the oxygen utilization of tissues from animals injected with these compounds and of a specific rat-heart homogenate system to which these substances have been added

Rall and his co-workers[70i] studied the metabolism of radioactive triiodothyronine L-thyroxine and D-thyroxine in subjects with and without thyroids and in one individual with a complete biliary fistula They found that the optical isomers of thyroxine were metabolized at markedly different rates although they were distributed in a similar manner in the body fluids whereas triiodothyronine was metabolized at a much faster rate than L-thyroxine and although initially it was distributed in a space similar to that of thyroxine the final value of distribution exceeded the body weight Keating and Albert[0k] compared the distribution and metabolism of radioactive triiodothyronine with that of radioactive L-thyroxine by injecting physiological doses of either compound into immature rats Both substances were distributed immediately and identically in the liver and were similarly massive in

decay to range from 0.2 to 0.4 mg of thyroxine daily indicating that the same amount would be required to maintain a normal basal metabolic rate in a patient with complete myxedema Thompson and his co-workers[8] later found that 0.3 to 0.4 mg daily of thyroxine was in fact the necessary maintenance dosage in such patients

The duration of action representing the total period of incubation activity and decay varies to some extent in accordance with the method of measurement the manner of administration and the form and amount of the hormone utilized Thus Gaddum[83] found thyroxine to be effective for 3 days when given intravenously and for 3 weeks when administered subcutaneously Salter Lerman and Means[84] found thyroxine polypeptide to be effective for 90 days *whether given orally or* intravenously Thompson found intravenous thyroxine active over a period of 90 days and desiccated thyroid over a period of 69 days Hughes[86] has measured the duration of action of single doses of thyroxine and desiccated thyroid in rats pre treated with thiouracil This drug prevents synthesis of thyroid hormone and results in compensatory hyperplasia and lowered iodine content of the thyroid Administration *of thyroxine or desiccated thyroid will prevent these* effects and therefore the duration of their actions may be measured by ascertaining the onset of hyperplasia through the determination of increased gland weight Hughes observed much shorter duration of action even with large doses than the majority of previous investigators Small doses lasted 3 to 12 days and large doses given intra peritoneally were completely metabolized within one month Subcutaneous or intravenous injections of thyroxine were effective for as long as thyroid powder by mouth He believes this method is more accurate in measuring duration of action of thyroid hormone than the basal metabolic rate Reineke and his co workers[87] have also found this technique comparable with the standard metabolic method of performing thyroid assays or measurements of thyroid function (Figs 4 and 5)

The metabolism of thyroxine has been more carefully studied since 1944 when Joliot and his associates first described the preparation of radioactive thyroxine and its behavior in the organism[8] [8b] Albert and his co-workers[5] [5d 6] have investigated the role of the gastro intestinal tract and the liver in the metabolism of radiothyroxine by the intravenous injection of physiological doses of radioactive L thyroxine into immature male rats They observed an immediate distribution of the injected material in the blood (38 per cent of the dose) the liver (30 per cent) and the remaining tissues of the body (32 per cent) After this initial

of thyroxine The organic iodine content of the whole thyroid gland is due almost entirely to thyroxine and diiodotyrosine The calorigenic action has been claimed by Means and his associates [75, 76] to depend upon this total organic iodine rather than upon thyroxine content alone On the other hand, Palmer and Leland [77] concluded that thyroxine alone determined the calorigenic effect of thyroid, and they were able satisfactorily to explain the apparent correlation between total organic iodine of the thyroid and calorigenic activity reported by Hunt and Krogh and Lindberg [8] as due to a fortuitous parallelism between total and thyroxine iodine content Subsequently, McClendon, Foster, and Cavett, [79] after studying the calorigenic action of thyroglobulins with varying thyroxine content upon the metabolic rate of rats, concluded that the calorigenic effect of thyroglobulin depended on its thyroxine content alone Harington [60] also expresses doubt concerning the adequacy of the evidence relating the activity of the thyroid gland to its total iodine content rather than to its thyroxine iodine content

Two aspects of thyroid physiology common to all its actions are the phenomena of latency of activation and decay These manifestations are apparent either following the administration of the hormone to the thyroid less individual or following removal or atrophy of the gland When thyroxine is administered intravenously to the hypothyroid subject no discernible effect is seen until about 12 hours have elapsed [80] Following this period there develops an increased rate of metabolism which reaches a maximum on the fourth day and then gradually declines over a period of 4 to 6 weeks to the initial level The curve of activation and inactivation or decay following a given dose of thyroxine or dried thyroid gland follows a definite pattern which may be expressed mathematically with some accuracy Briefly, these curves are exponential rather than arithmetic and indicate that crystalline thyroxine must be activated before it can function The phases of activity of thyroxine in dried thyroid may therefore be divided into these three, according to Boothby (1) the period of incubation, (2) the period of increased activity, and (3) the period of decay

When the thyroid gland is removed or undergoes spontaneous atrophy, progressive inactivation or decay of the hormone takes place The same phenomena may be observed when thyroid medication is discontinued in a myxedematous patient who has received sufficient thyroid to maintain a standard metabolic rate The rate of inactivation is exponential and follows a gently sloping curve which takes 70 to 80 days for completion Plummer and Boothby [81] found the daily rate of thyroxine

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distribution, rapid diffusion occurred into the gastro intestinal tract, chiefly by way of bile but probably also by direct secretion At equilibrium the gastro-intestinal tract contained at any time about one half of the circulating radiothyroxine or intermediates thereof A massive recirculation of radioactivity occurred from the bowel, presumably via the portal and lymphatic drainage The rapidity of the recirculation was

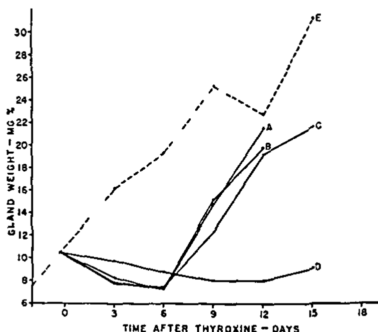


Fig 4 A comparison of the effect of single doses of thyroid hormone given by various routes to thiouracil treated rats A = 1 mg thyroxin in solution intravenously B = 500 mg desiccated thyroid by stomach tube C = 1 mg thyroxin in solution subcutaneously D = 1 mg thyroxin suspension subcutaneously E = control animals receiving thiouracil alone The initial point indicates the gland weight at the beginning of thiouracil treatment and 0 the time of thyroid hormone administration Each point represents the average of 5 or more animals From Hughs A M Endocrinology 1945 xxxvii 80 85

emphasized by the disparity between the rate at which radioactivity was secreted into the bowel, more than 100 per cent per hour, and the rate at which it left the bowel in the feces, about 3 per cent per hour Two thirds of injected radiothyroxine was ultimately excreted in feces and one third in urine Thyroxine or some derivative of it was slowly removed from blood by fixation in tissues, particularly the liver Such fixation also occurred in kidney and in other tissues at a rate of about

1 per cent per hour More than one half of the residual radioactivity was in the liver 16 days following injection

The proportion of endogenously I^{131} labeled thyroid hormone in the thyroid carcass gastro-intestinal tract and liver and the rates of movement of labeled hormone in these compartments and in the excreta

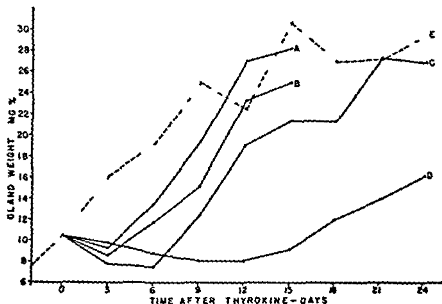


Fig 5 Effects of a single injection of thyroxin on the rate of enlargement of the thyroid glands of thiouracil treated rats A = 10 ug (solution) B = 100 ug (solution) C = 1 mg (solution) D = 1 mg (suspension) E = control animals, receiving thiouracil alone The initial point indicates the gland weight at the beginning of thiouracil administration and 0 the time when thyroxin was injected Each point represents the average of 5 or more animals From Hughs, A M Endocrinology 1945 xxxvii 280-85

were next determined under conditions of experimentally altered thyroid function in immature rats The thyroids of these rats were labeled with I^{131} and then exposed to agents or procedures that caused either liberation or retention of labeled hormone The proportions of I^{131} in the thyroid gastro-intestinal tract and carcass were determined Thiouracil caused an intense loss of thyroidal I^{131} and a symmetrical increase in I^{131} of the gastro intestinal tract and carcass Thyrotrophin induced similar but less intense loss of thyroidal I^{131} and a symmetrical gain in I^{131} of the carcass and gastro intestinal tract Hypophysectomy or

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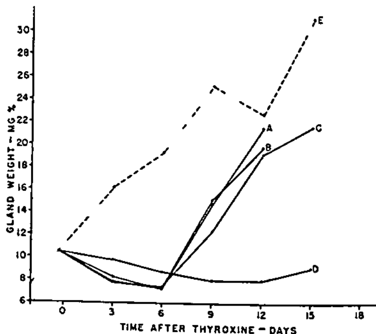


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equilibrated with serum iodide and is present as only a small percentage of the total serum iodine partly because it is disposed of rapidly and partly because its volume of distribution is comparatively large The liberated iodide present in blood is eliminated mainly in the urine Thyroid hormone is not accumulated by the thyroid and reutilized Iodide liberated in the catabolism of thyroid hormone is reaccumulated and reutilized in a normal person Approximately o per cent of the liberated iodide would be accumulated by the normal thyroid The iodide of dietary origin probably accounts for far more of the iodide utilized by the normal thyroid for synthesis of new thyroid hormone than does the small porportion of iodide liberated from the catabolism of thyroid hormone which is reaccumulated

In a later study [81] radiothyroxine was injected intravenously as a single dose in 6 patients with exophthalmic goiter The initial phase of disappearance from the blood was very rapid with a half value time of 3 hours After 12 or more hours a slow disappearance with a half value of 5 to 6 days became apparent presumably due to utilization of the thyroxine by the tissues and excretion in the urine and feces Uptake by the thyroid and excretion in the urine after administration of radio thyroxine were slower than after administration of radio-iodine and appeared to depend for the most part on the rate of release of radio iodine from radiothyroxine In these patients too the main metabolic fate of thyroxine aside from some excretion in the feces and the urine was de iodination Part of the iodide thus released was reaccumulated in the thyroid and part was excreted in the urine depending upon the ratio of the thyroidal clearance and the renal clearance About one third of the injected hormone was metabolized in 24 hours

The physiological effects of the hormone will now be considered in detail The differential analysis of its effects should not obscure the fact that in the patient the actions are multilateral and simultaneous involving many tissues and organs

Oxidative and Calorigenic Action

The first observation of the calorigenic effect of thyroid was made by Magnus Levy in 1895 when he demonstrated that thyroid deficiency was associated with a reduced metabolism and lowered oxygen consumption [88] The fundamental oxidative processes of the body and minimal heat production are cellular phenomena which proceed independently of

treatment with thyroglobulin produced a marked increase in thyroidal I^{131} and a marked and asymmetrical decrease in the extrathyroidal I^{131}, a greater decrease occurring in the gastro intestinal tract than in the carcass. Thus there exists a wide range over which the excretion of I^{131} from the body is proportional and in equilibrium with the secretion or loss of I^{131} from the thyroid. When liberation of thyroidal I^{131} is inhibited by therapy with thyroglobulin, the excretion of I^{131} in feces and urine is correspondingly inhibited. However, when liberation of thyroidal I^{131} is accelerated by thiouracil the fecal and urinary excretion of I^{131} is also accelerated but does not keep pace with the liberation of I^{131} from the thyroid. There appears to be a ceiling beyond which the body cannot further excrete labeled thyroid hormone.

Klitgaard[8f] on the other hand, in studies of the biliary and urinary excretion of radio iodine following subcutaneous injection of tracer amounts of I^{131} labeled thyroxine in normal, hypothyroid and hyperthyroid rats, found that thyroidectomized and thiouracil treated groups showed reduced biliary radio-iodine elimination, as well as diminished bile volume during the 6 hour collection period. Hyperthyroid animals showed a marked increase, thiouracil treated animals a decrease in urinary excretion of radioactive iodine over a 12-hour period. The radio iodine excretion in both bile and urine tended to be lower in the thiouracil treated rats than in the thyroidectomized groups.

The metabolism of thyroxine has also been studied in human subjects with normal decreased and increased thyroid function[87g, 87h, 87i, 87j]. Albert and his associates[8h, 87i] have studied the metabolic behavior of racemic radiothyroxine administered orally or intravenously to patients with myxedema maintained in a euthyroid state with non labeled racemic thyroxine. Forty one per cent of the radioactivity was excreted in the urine and 12 per cent in the feces. Eighty-five per cent of the urinary I^{131} was present as inorganic iodide and 15 per cent as organic I^{131}, consisting of both thyroxine and diiodotyrosine. The bulk of thyroid hormone is therefore de iodinated and excreted in the urine as iodide. On the basis of these studies Albert and his co workers formulated the following highly tentative picture' of the metabolism of thyroxine under normal conditions. On entry into the circulation thyroxine is confined at first to the plasma from which it is transferred to the tissues of the body, including especially such organs as the liver, and becomes equilibrated with the thyroid hormone already present in tissue. In the tissues thyroid hormone is catabolized mainly to iodide and to a minor extent is split apparently at its ether linkage. The iodide liberated becomes

The calorigenic action of the thyroid hormone has been clearly traced to the tissues but the exact mechanism by which it alters metabolic processes is unknown It is probably not a true catalyst because it lacks uniformity of effect among various tissues and because its effect is delayed in appearance Both Gordon and Heming and earlier Dye[93] suggested that it works by increasing the effectiveness of or by stimulating the synthesis of various respiratory enzymes

Thyroid in Thermoregulation

In its oxidative function the thyroid contributes significantly to total heat production In addition the gland has a definite relation to the actual regulation of the body temperature Prolonged exposure to cold results in increased thyroid activity[94] This has been most satisfactorily demonstrated by measuring the fixation of radio iodine in the rat s thyroid following exposure to varying temperatures[95] Exposure to freezing temperatures (0 to 2) produced thyroid stimulation after 7 days which reached a maximum after 26 days and was absent after 40 days There was a nearly threefold increase in the uptake of radio-iodine for thyroxine synthesis at the time of maximal stimulation by the cold Heat lessened thyroid activity but the effect of heat was far less prominent than that of cold

The thermoregulatory function of the thyroid is dependent upon both the hypophysis and the adrenals According to Uotila[96] hypophysectomy abolishes the response of the thyroid to cold Epinephrin has a calorigenic effect which is greatly increased by the thyroid hormone[94] Dinitrophenol in amounts calorigenically equal to thyroxine increased the hypothermia of mice subjected for 1 hour to an environmental temperature of 5 C whereas thyroxine decreased such hypothermia[97]

The role of the thyroid in thermoregulation is also reflected in changes in the gland occurring seasonally Riddle[98] found the thyroid of pigeons to be larger in winter and smaller in summer Earlier Seidell and Fenger[99] demonstrated a threefold increase in iodine content of the thyroid gland of various animals during the summer months thus indicating reduced physiological activity Kendall and Simonsen[100] similarly found increased iodine and thyroxine content of the gland during the summer and a decrease during the winter Dempsey and Astwood[101] have determined the rate of hormone secretion at various environmental temperatures by measuring the amount of thyroxine

thyroid activity, but the thyroid, in the words of Marine, provides the means through its iodine-containing hormone, of maintaining a higher level of metabolism than would otherwise obtain'[89] In other words, the thyroid forces an increased rate of oxidation within the cell There is production of heat with oxidation, and thus the oxidative effect of thyroid is known as its calorigenic action

The calorigenic action of thyroid may be readily measured in the organism by the determination of oxygen consumption or carbon dioxide production This is the method of indirect calorimetry and is the basis of clinical metabolism testing wherein the oxygen consumption is measured for an exact unit of time and compared with standard values for normal individuals One may however, with a calorimeter measure the heat production of the organism by utilizing the method of direct calorimetry, this is too cumbersome for clinical purposes but has been of fundamental importance in research on energy metabolism

In the resting fasting state the thyroid accounts for slightly less than half of the total heat output or oxygen consumption, since total thyroidectomy or myxedema decreases the basal metabolic rate by about 40 per cent The organism lives and respires but the oxidative fires burn low

That the thyroid hormone produces its calorigenic effect by direct action on the tissues or the tissue cells has been established in many ways Aub and his associates[90] showed that the hypermetabolism induced by thyroxine could not be explained by muscular activity or tonus and was unaffected by adrenalectomy Studies on the whole animal because they are complicated by nervous and interhormonal relationships have to some extent been supplanted by observations on excised organs or tissues in further efforts to understand the exact way in which the thyroid exerts its oxidative effect

Myer McTiernan and Aub[91] showed that liver slices from thyroxinized mice had an increase in oxygen consumption and in anerobic glycolysis They also demonstrated that the oxygen consumption of denervated and normal kidneys is similar in thyroxinized dogs The nervous system is thus not essential for the effect of thyroxine on tissue metabolism The direct effect of thyroxine upon tissues is not universal since these same workers found no effect or a depressing effect on the oxygen consumption of malignant tissues excised from thyroxinized mice In similar fashion Gordon and Heming[9] found that administration of thyroid and thyroxine caused significant increases in the oxygen consumption of liver kidney diaphragm and heart of the rat but they observed no effect on spleen, brain or testis

The calorigenic action of the thyroid hormone has been clearly traced to the tissues but the exact mechanism by which it alters metabolic processes is unknown It is probably not a true catalyst because it lacks uniformity of effect among various tissues and because its effect is delayed in appearance Both Gordon and Heming and, earlier Dye[93] suggested that it works by increasing the effectiveness of or by stimulating the synthesis of various respiratory enzymes

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necessary to maintain normal thyroid weight in thiouracil treated rats. With this method there was further confirmation of the view that cold increases thyroid activity and hormonal synthesis while heat does the reverse. Similarly Turner and Turner,[10] utilizing the Warburg technique showed that the same was true when the thyroid tissue of guinea pigs was studied in vitro. Mansfeld[103] has recently summarized studies which, if confirmed, would establish the thyroid gland as of ascendent importance in thermoregulation. By serum transfer experiments he showed that temperature regulation against heat and cold was associated with the secretion of substances which depressed oxidation in normal animals and was dependent on an intact thyroid gland. He found the thyroxine sensitivity of the organism greatly decreased during the spring and summer; thyroidectomy abolished this sensitivity. Two crystalline substances, thermothyrin A and B, were isolated from the gland. Thermothyrin A was produced throughout the whole year if the organism was exposed to high temperatures, whereas thermothyrin B was produced during the summer months regardless of external temperature. Both of these substances were antithyroidal in their action.

Effect on Growth and Metamorphosis

The precise role of the thyroid in growth is not entirely clear because of its interrelation in this function with the anterior pituitary. In human and animal cretinism stunting of growth regularly occurs, yet there is much evidence that the thyroid hormone serves an auxiliary rather than a primary function in growth. Rats and goats thyroidectomized in the first week of life quickly become static in weight and anatomical differentiation and present the usual features of cretinism.[104, 10, 106] The effects of thyroidectomy appear earlier and are more pronounced in accordance with the age and weight of the animal. Rats thyroidectomized at birth showed marked retardation of growth and maturation but according to Scow and Simpson[107] did not develop the growth stasis reported by Salmon.[104, 10] Instead they showed a very slow but continuous increase in weight and skeletal size. In addition these workers noted delayed appearance of secondary ossification centers, low oxygen consumption, retarded change from infant to adult type of hair, delayed opening of the eyes, and delayed eruption of the teeth (Figs. 6 and 7).

Growth in the thyroidectomized animal can be maintained or restored

to normal by the administration of thyroid gland substance[108] thyroxine[109] or artificial thyroprotein[106]

The administration of anterior pituitary extract to rats thyroidectom-



Fig 6 Triplet kids Center animal normal right and left hand animals thyroidectomized at 10 days old Photograph taken 13 weeks after operation (Sutherland Simpson) From Harington C R The thyroid gland its chemistry and physiology Oxford University Press, London 1933

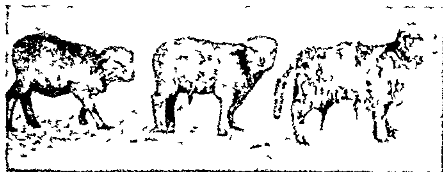


Fig 7 Three lambs thyroidectomized at the age of 3 4 weeks Note pot belly of left hand animal and poor condition of fleece in all Photograph taken 8 weeks after operation (Sutherland Simpson) From Harington C R The thyroid gland its chemistry and physiology Oxford University Press London 1933

ized at birth will not induce gain in weight skeletal growth, or gonadal development, according to Salmon[110] Her view is that the thyroid is necessary in the early postnatal period for the development of the capacity of the organism to respond to other hormones that influence growth The age of the animal at the time of thyroidectomy is therefore a critical factor, since it is established that anterior pituitary extract is effective in promoting the growth of animals thyroidectomized in the later postnatal period[111] Rowlands[109] has also noted the failure of pituitary injection to overcome growth retardation in the very young thyroidectomized animal Scow and Simpson,[11] utilizing thyroidectomized newborn rats, found that the response to hypophyseal extracts did not depend upon the age of the animal and that the capacity to grow with pituitary stimulation alone was present at birth

The role of the thyroid in growth is apparently that of a synergism to the more important stimulation provided by the growth component of the anterior pituitary This synergism was first observed by Smith[113] who noted greater growth with pituitary and thyroid extracts than with the former alone in hypophysectomized and thyroidectomized rats The synergistic action of thyroid on growth has been confirmed by Evans and his co-workers[11, 114] who observed abnormally large growth increments when thyroxine was administered with anterior pituitary extract to thyroidectomized animals They also found that thyroid did not stimulate growth in animals deprived of both hypophysis and thyroid gland thus again indicating the primacy of the anterior pituitary in growth Additional proof of the synergy between thyroid and hypophysis in the growth process is evidenced in the increased growth rate of normal young mice given thyroxine[11] or thyro active iodo casein[116] and in the increased speed of growth in juvenile thyrotoxicosis[117]

Growth involves either increase in cell size or cell number or both The end result of growth will therefore be a larger or a more differentiated organism The thyroid plays a significant role in these processes, but more so in differentiation than in growth Gudernatsch,[118] while studying metamorphosis in tadpoles observed that thyroid accelerated this process in a remarkable fashion This observation was confirmed by Uhlenhuth[119] who found that small quantities of thyroglobulin led rapidly to precocious metamorphisis of tadpole larvae Later Allen[120, 121] demonstrated that thyroidectomized tadpoles will not metamorphose Finally thyroid was found to induce the metamorphosis of axolotls, which usually remain in the larval condition without further matura

tion[1] These striking effects of thyroid upon differentiation result essentially in the induction of precocious growth

The influence of thyroid upon differentiation is both so specific and so sensitive that it may be used for detecting thyroidal activity in biological materials through measuring metamorphosis of either tadpoles or axolotls[1-3]

Thyroid and Water Exchange

Knowledge of the relation of the thyroid to water exchange has been accumulated chiefly through studies on myxedematous patients and thyroidectomized animals because the effect of the thyroid hormone on water metabolism is so clearly seen during the initial phase of its administration to the hypothyroid subject

In myxedema there occurs a low plasma volume[1,4,3,5] and an increased plasma protein associated with an increase in extracellular fluid in the tissues generally whereas in thyrotoxicosis the blood volume is increased[1,6] The increased tissue fluid that characterizes myxedema differs from all other types of edema fluid in that it has a high content of a mucinous protein Boothby and his co workers[1,7] after studying the effects of thyroxine administration upon the nitrogen metabolism of normal and myxedematous subjects concluded that the edema fluid in myxedema had twice the protein content of serum This extra protein they regarded as reserve or deposit protein and found it to be eliminated or oxidized when thyroid was administered Along with this protein diuresis following thyroid administration there occurs a diuresis of water of considerable magnitude The fluid so diuresed contains a large excess of sodium over potassium and Byrom[1,8] has therefore concluded that the fluid is contributed mainly by the extracellular compartments of the body In the normal subject thyroxine causes loss of body protein associated with loss of water containing more potassium than sodium and so presumably derived from the intracellular water stores This simple view of the relative roles of potassium and sodium in intracellular and extracellular water exchange has however been criticized in a general way by Darrow[1,9] who notes that these ions are also in a dynamic state in which no part of the body is inaccessible to them The least we can do is to cease speaking of the distribution of various ions as if they were always excluded from certain phases of body water

Another factor contributing to the increased tissue fluid and decreased plasma volume of myxedema is the great increase in capillary perme-

ized at birth will not induce gain in weight skeletal growth, or gonadal development, according to Salmon[110] Her view is that the thyroid is necessary in the early postnatal period for the development of the capacity of the organism to respond to other hormones that influence growth The age of the animal at the time of thyroidectomy is therefore a critical factor, since it is established that anterior pituitary extract is effective in promoting the growth of animals thyroidectomized in the later postnatal period[111] Rowlands[103] has also noted the failure of pituitary injection to overcome growth retardation in the very young thyroidectomized animal Scow and Simpson,[11] utilizing thyroidectomized newborn rats, found that the response to hypophyseal extracts did not depend upon the age of the animal and that the capacity to grow with pituitary stimulation alone was present at birth

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depletion The important factors for consideration are three acidosis and negative nitrogen balance a catabolic effect of thyroid hormone on bone, and the possibility of an associated hyperparathyroidism

A negative nitrogen balance and tissue acidosis may cause hyper calcinuria Many thyrotoxic patients have a negative nitrogen balance and this fact must be contributory in some instances With a negative nitrogen balance there is increased phosphate and sulphate excretion as the patient is burning body protein and thus has the equivalent of an acid forming diet[13, 138] *which in itself increases calcium excretion* The negative nitrogen balance produced by fasting causes urinary calcium excretion comparable to that of hyperthyroidism

A secondary cause of calcium depletion in thyrotoxicosis is the possible catabolic effect of thyroid hormone on bone It is true that the calcium loss is far greater proportionally than the rise in metabolic rate and that there is no calcium loss in non thyrogenous hypermetabolism These facts do not exclude a direct effect of the hormone on calcium deposits in the bone and in truth one is still left with this mechanism as the best explanation of the disturbed calcium metabolism[13]

Finally to be considered is the hypothesis of an associated hyperpara thyroidism in all cases of thyrotoxicosis Clinically this association rarely occurs[137] Hansman and his associates[138, 139] have argued that the increased calcium and phosphorus excretion in thyrotoxicosis is due to concomitant hyperparathyroidism for these reasons (1) there is com plete lack of parallelism between the basal metabolic rate and calcium phosphorus exchange (2) roentgen ray therapy to the hyperplastic thyroid alters the calcium phosphorus balance favorably while leaving the metabolic rate unaffected, because of the greater sensitivity of the parathyroids to irradiation This is an argument of indirection which may be valid and yet if true is contrary to the usual finding of hyper calcemia in proved hyperparathyroidism In a study of parathyroid function in hyperthyroidism utilizing the rise in serum calcium of the rabbit as the method of assay, Gilligan Volk and Gargill[140] found evidence of parathyroid hyperfunction in less than half the cases studied Cope and Donaldson[141] were able to demonstrate a marked increase in calcium and phosphorus *excretion in a patient with coexistent hypo* parathyroidism and thyrotoxicosis If parathyroid activity is increased in hyperthyroidism its physiological pattern of activity is probably some-what different from that seen in hyperparathyroidism alone The different pattern of response to thyroid and parathyroid hormone has again been emphasized by Logan Christensen, and Kirklin[14] who found that in

ability demonstrated by Langer[130] in this disease This altered permeability is returned to normal by thyroid administration, indicating that the hormone helps maintain normal capillary permeability

Thyroid Hormone and Mineral Metabolism

The effect of the thyroid hormone on calcium and phosphorus metabolism has been extensively studied Many early investigations suggested an excessive calcium and phosphorus loss but were inconclusive because of failure to control the intake In 1910 Towles[131] clearly demonstrated that thyrotoxic patients with a negative nitrogen balance also had a loss of calcium Aub and his co-workers,[132, 133] however, in more comprehensive studies of this subject, conclusively established the marked increases in both calcium and phosphorus excretion in toxic goiter The percentile increased loss was far greater than the increased basal metabolic rate, and elevated metabolic rates from other than thyroid disease were not associated with increased calcium and phosphorus excretion The ratio of excretion of calcium to phosphorus strongly suggested that the extra loss came from calcium phosphate in the bones This was further corroborated by roentgenological evidence of bone demineralization In myxedema, on the other hand, there was marked decrease in calcium excretion These profound changes in calcium and phosphorus exchange in thyrotoxicosis did not alter the blood levels of these minerals

The increased calcium and phosphorus excretion in thyrotoxicosis occurs both through the kidneys and through the intestines and is reflected in elevated urine and fecal values This contrasts strikingly with the mineral exchange in hyperparathyroidism, where the increased excretion is entirely through the kidneys A satisfactory explanation of the large fecal calcium in thyrotoxicosis has been offered by Althausen and his co workers[134] who studied calcium exchange in the rat s intestines They concluded that in experimental hyperthyroidism there was interference with normal reabsorption of intestinally excreted calcium This was ascribed to two factors (1) the increased food ingestion usually occurring in thyrotoxicosis interferes with normal reabsorption, and (2) increased intestinal peristalsis accelerates the passage of feces to such an extent that there is further interference with reabsorption

As the heightened excretion of calcium and phosphorus occurs in the urine as well as in the feces other mechanisms must exist that cause this

magnesium was low or absent This change in magnesium partition was not associated with changes in the total serum magnesium

These findings were confirmed and extended by Dine and Lavietes [1] who felt that the serum level of the bound magnesium might be a useful index of thyroid function They suggested further that the magnesium might be attached to the thyroid hormone or be part of an associated enzyme system This interesting development has failed of confirmation by Cope and Wolff [1 3] and Bissell [154] who found no important deviation from normal in the magnesium partition of hyperthyroid subjects

The studies on magnesium partition in thyroid disease have suggested that bound magnesium unlike bound calcium is physiologically active but this knowledge has as yet no practical applications

Thyroid and Protein Metabolism

The role of the thyroid hormone in protein metabolism in normal persons has not been determined Chief attention has been given to the nitrogen balance in myxedema and thyrotoxicosis and to the alterations in creatine and creatinine metabolism occurring in these conditions If adequate calories from carbohydrate and fat sources are available thyrotoxic patients may be maintained on low protein diets with the minimal nitrogen excretion characteristic of normal persons [155]

In thyrotoxicosis urinary nitrogen is increased [1 6] whereas it is decreased in myxedema [157] Important changes also occur in creatine and creatinine metabolism Creatine is normally low or absent in the urine of adults on creatine free diets but in hyperthyroidism it is excreted in abnormal amounts Shaffer [1 8] who first noted this alteration also found decreased creatinine excretion in the same group of patients Both of these changes have been confirmed by many later investigators [158 16] The creatinuria disappears with control of the hyperthyroidism by iodine [161] although the altered creatine metabolism may persist for many weeks following thyroidectomy [16] In myxedema as in normal persons there is no creatinuria but evidence of abnormalities of the creatine metabolism is adduced by the fact that the spontaneous creatinuria of normal children is reduced or absent in cretinism and juvenile myxedema [163 164 165]

Richardson and Shorr [1 6] and later Thorn [16] found a decreased tolerance to ingested creatine in thyrotoxicosis and an increased tolerance in myxedema suggesting a fundamental alteration by thyroid activity in

hyperthyroid dogs there was a marked increase in renal calcium excretion with normal serum calcium levels and an inconsistent effect on phosphorus metabolism. The parathyroid hormone, on the contrary, caused an immediate rise in urinary phosphorus with a drop in serum phosphorus and a slow rise in serum calcium and calcium excretion.

Robertson[143] rejects the hypothesis of coexisting hyperparathyroidism, first on the ground that in his observations serum calcium tends to be low rather than high in thyrotoxicosis, and secondly because of the normalizing effect of iodine and thyroidectomy upon calcium excretion. He advances the theory that thyroid hormone typically lowers the renal threshold for calcium by direct action on the kidney. The lowering of the threshold results in a fall in serum calcium concentration, which causes an increased mobilization of calcium from the bones in the blood stream. In hypothyroidism, conversely, the renal threshold is raised and there is a subnormal excretion of calcium. This is an attractive theory based upon rather small differences in serum calcium levels between normal subjects and thyrotoxic patients.

Regardless of the mechanism there is no question of the fact of calcium and phosphorus loss in thyrotoxicosis. This is further evidenced in skeletal demineralization which can be demonstrated by roentgen ray examination of the bones.[144] Osteoporosis is not an invariable accompaniment of the thyrotoxic state except in long standing cases.[14] In addition the age of the patient[146] and the opportunity of achieving calcium and phosphorus balance by adequate mineral and vitamin D intake are factors of importance.[147] Osteoporosis may be severe enough to result in spontaneous fractures[14, 148] or so slight that it can be detected only by simultaneous radiograms of the normal and the thyrotoxic patient on the same x ray film.[13] In most patients it cannot be demonstrated.[147]

The large excretion of calcium and phosphorus in toxic goiter led Tibbetts and Aub[149] to investigate magnesium metabolism in that disease. Magnesium like calcium is present in small amounts in the blood and is also a constituent of bone. These authors found no increased magnesium excretion in two patients with thyrotoxicosis but they did not study the concentration of magnesium in the serum. Subsequently Soffer and his associates[150, 151] investigated the magnesium content of the blood in hyperthyroidism with special reference to the ratio between diffusible and bound or non diffusible fractions. They found a definite increase in the bound magnesium in 3[illegible] out of 50 cases of Graves disease. Treatment with iodine or thyroidectomy caused marked lowering of the bound magnesium and in myxedema, clinical or experimental the bound

tion of thyroid for a short period led to temporary diabetes or to permanent diabetes if the administration was long continued In the latter instance irreversible changes in the beta cells of the islets of Langerhans were demonstrable Houssay also found that islets previously damaged by antero hypophyseal injections were more sensitive to thyroid treatment However the diabetogenic action of thyroid was not as great as that of alloxan or anterior pituitary extracts since it did not take effect until there had been diminution in the pancreatic mass or actual damage to the islets This diabetogenic action continued after removal of the gonads thyroid and adrenal medulla In animals already diabetic as in human beings thyroid ingestion always increased the severity of the disease and shortened survival by increasing glycosuria ketonuria and insulin need

Thyroid feeding in rats can sensitize the islets to the diabetogenic action of alloxan according to Martinez [1] whose figures are of interest there was an average lethal dose of -5 mg of alloxan for the hyperthyroid rats of 54 mg for the controls and of 74 mg for the thyroidectomized animals showing the increased resistance to the drug in hypothyroidism

This problem has been approached by Soskin [173] in a different fashion Through the use of hypophysectomized dogs he was able to avoid the difficulties of attempting total thyroidectomy in dogs who often have aberrant thyroid tissue Secondary atrophy of the thyroid resulted from hypophysectomy and with it was a marked hypoglycemia in the fasting state Administration of thyroxine restored and maintained normal blood sugar values thus proving that this secondary atrophy plays a significant role in the carbohydrate disturbance following hypophysectomy Herring and his co-workers [174] however found no such effect of thyroxine on the blood sugar and glycogen stores of fasted hypophysectomized rats and Lukens and Dohan [175] using partly pancreatectomized cats found no great effect of thyroxine or thyrotropic hormone on carbohydrate metabolism and no modification of diabetes by thyroidectomy There are apparently great species differences with regard to the effect of the thyroid on carbohydrate metabolism

The second effect of the thyroid in relation to carbohydrate metabolism is found in its specific action in altering the absorption of sugars from the intestinal tract Thyroid ingestion in normal rats causes greatly increased absorption of glucose while thyroidectomy causes a reduced rate of absorption [1 6] This increase is probably due to a direct action on the mucosa of the digestive tract with stimulation of phosphorylation This is the important intermediary step in the conversion of starch or glycogen

the capacity of the organism to metabolize creatine Tierney and Peters [166] however, could detect no important change in creatine metabolism, though agreeing that hyperthyroidism induces or increases creatinuria They found that creatine, unlike creatinine had a definite renal threshold above which excretion into the urine occurred In thyroxinized rats Bodansky [167] and Sure [168] have demonstrated marked reduction in muscle and heart creatine content, and more recently Wang [169] observed in rabbits that thyroxine treatment reduced muscle creatine and phosphocreatine content and that thyroidectomy produced opposite effects Wang also found that thyrotoxicosis induces excess creatinuria but that this was transitory and soon decreased and approached normal levels At the same time creatinine elimination in the urine was very much reduced probably owing to a creatine-sparing process He points out that these relations of urinary creatine and creatinine are important in explaining the lack of correlation between the level of the basal metabolic rate and creatinuria and they eliminate the possibility of utilizing creatinuria as a measure of the thyrotoxicosis

Wilkins and Fleischman [170] on the basis of careful human experiments, concluded that the essential action of thyroid is creatinolytic, it facilitates loss of creatine from the muscles and liberates it in excess, thereby diminishing the stores of creatine and phosphocreatine Thus metabolic conversion in thyrotoxicosis proceeds through normal channels but at an accelerated rate In myxedema there is storage of creatine and phosphocreatine in the muscles

Thyroid and Carbohydrate Metabolism

The occurrence of glycosuria and hyperglycemia in thyrotoxicosis as well as the aggravation of diabetes by thyroid overactivity and its amelioration by thyroidectomy, have led to many studies on the relation of the thyroid hormone to the metabolism of carbohydrates This relation is manifold and occurs primarily through (1) direct and specific action on the pancreas (2) alteration of intestinal absorption (3) changes in the body glycogen stores and (4) increased carbohydrate utilization by the tissues

The action of the thyroid on the pancreas has been most informatively studied by Houssay [171] in dogs An extreme degree of thyroid feeding to these animals did not produce diabetes when there was an intact pancreas Following subtotal pancreatectomy, however, similar administra

just as it plays a role in protein and carbohydrate metabolism Epstein and Lande[185] observed an increase of the blood cholesterol in myxedema and a decrease in hyperthyroidism Hurxthal and his associates[186, 187, 188, 189] confirmed and extended these observations firmly establishing the important effect of thyroid hormone upon cholesterol levels in the blood The cholesterol concentration was found to be an especially sensitive indicator of hypothyroidism whereas the deviations produced by hyperthyroidism were less constant Following total thyroidectomy for *chronic heart disease*[190] *appreciable rises in the blood cholesterol occurred* within 1 week increasing steadily to maximum values at the end of 4 weeks In this group of patients the cholesterol was at times a more accurate measure of myxedema than the basal metabolic rate This has also been our experience in spontaneous myxedema In the evaluation of juvenile hypothyroidism the determination of blood cholesterol has been of value[191] especially in view of the difficulties encountered in determining the basal metabolic rate in children

Alterations in the concentration of blood cholesterol reflect parallel changes in all the lipids of the blood cholesterol determination serving as a convenient measure of these changes because it is readily estimated in the laboratory The total lipids of the blood include neutral fat fatty acids free cholesterol cholesterol esters and phospholipids Bing and Hechscher[19] found an increase in the total lipids in myxedema and a decrease in hyperthyroidism Boyd and Connell[193, 194] studied the effect *of hyperthyroidism in fat metabolism by careful fractionation of the* blood lipids and found significant decrease in all of the lipids except neutral fact which remained unchanged The lipid values returned to normal with control of the thyrotoxic state In a study of the serum lipoids particularly cholesterol phosphatides and fatty acids in hypothyroidism Gildea Man and Peters[195] found these fatty constituents of the blood readily affected by changes in the amount of thyroid hormone Myxedema was associated with high values which reverted to normal following thyroid administration These workers concluded that normal cholesterol values in the blood excluded the diagnosis of hypothyroidism

While the estimation of the cholesterol level of the blood has established itself as a valuable laboratory aid in the diagnosis of myxedema this procedure has been found less dependable in the diagnosis of thyrotoxicosis This is due to the considerable range of values found in normal persons a range so great that no significance can be attached to a single observation unless it is extremely abnormal However, the variability

to glucose, or the reverse in which phosphate is bonded to glucose The accelerated absorption of sugar readily explains the hyperglycemia the high glucose tolerance curves and the postprandial glycosuria found in thyrotoxicosis In myxedema on the other hand the slow intestinal absorption of sugar leads to low sugar tolerance curves Thyroxine also acts to augment maximally the rate of glucose absorption by the renal tubules [177] where again it is believed to exert its effects by activation of the enzyme systems involved in the transfer of phosphate energy

The effect of thyroid on liver glycogen varies in accordance with the amount of food ingested and the store of glycogen present in the liver If thyroxinized animals eat adequately to maintain weight they will form and store glycogen [178] This may be dependent upon the intake of B vitamins since it has been demonstrated [179] that hyperthyroid animals receiving subminimal amounts of B vitamins will lower their glycogen reserves while maintaining normal glycogen storage on full intake of B vitamins The idea that thyroid makes liver glycogen labile depends for its proof upon the effect of epinephrin on liver glycogen since this hormone produces glycogenolysis more readily in hyperthyroid than in normal animals This is true but depends further on the liver glycogen stores [180] Epinephrin hyperglycemia in thyroxinized animals is exaggerated so long as glycogen is present in the liver but disappears with depletion of the glycogen stores it may even lead to hypoglycemia [181] Furthermore in like manner Long [180] has pointed out that the supposed antagonism of the thyroid hormone and insulin is dependent upon liver glycogen stores since thyroid extract decreases insulin hypoglycemia while liver glycogen is present but eventually leads to glycogen depletion and fatal hypoglycemia from minimal amounts of insulin The glycogen content of skeletal and cardiac muscle has also been shown to respond to the thyroid hormone in much the same way as does liver glycogen [18, 183] decreasing in amount with hyperthyroidism

Finally to be considered is the action of the thyroid in increasing the utilization of carbohydrate by the tissues Mirsky and Broh Kahn [184] using eviscerated animals showed that the extrahepatic tissues utilize more carbohydrate when thyroid is fed Thus in hyperthyroidism one may properly postulate an increased removal of glucose from the blood because of increased carbohydrate oxidation in the tissues

Thyroid and Fat Metabolism

The thyroid hormone influences the intermediary metabolism of fats

produces no changes in blood cholesterol[199] Similarly depression of the basal metabolic rate by non thyrogenous conditions is not accompanied by alterations in blood cholesterol levels [90] (Fig 8)

Animal experiments have not provided illuminating answers with respect to the mechanism by which blood fat levels are changed in thyroid disease In the dog thyroidectomy elevates the blood lipids [91] provided the nutrition of the animal is adequate [5] Hypophysectomy by itself has little effect but produces a high concentration of blood lipids when followed by thyroidectomy [13] In the monkey thyroidectomy has no measurable effect on cholesterol levels [94 90 96] The hypothyroid rat according to Handler [97] has a marked increase in liver cholesterol and a slight increase in neutral fat whether on a normal or a choline deficient diet Thyroid feeding reverses this process The effect of thyroid is most marked on the liver cholesterol fraction Handler believes that the thyroid may specifically control cholesterol metabolism through regulation either of its synthesis and utilization or of transport and distribution

Thannhauser and Schmidt [8] in a recent review of fat metabolism conclude that the reason for the increase of serum cholesterol in hypothyroidism is not known

Thyroid Function and Vitamin Metabolism

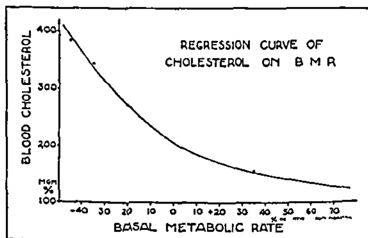
Just as the thyroid hormone plays an important role in the intermediary metabolism of proteins carbohydrates and fats so too has it significant interrelations with vitamin metabolism The large increase or decrease in energy metabolism occasioned by elevation or depression of the thyroid function in itself is contributory to this interplay because vitamin need in many instances runs parallel with energy metabolism Clinically the two outstanding examples of the effect of the thyroid on vitamin metabolism are seen in the striking deficiencies of vitamin B complex induced by thyrotoxicosis and in the disorder of vitamin A metabolism evidenced by the carotenemia of myxedema

Drill [99] has considered in great detail the relations between each vitamin and the thyroid gland Vitamin A and several components of the B complex have been most clearly related to changes in thyroid function Experimentally an antagonism between thyroxine and vitamin A has been demonstrated in amphibia Vitamin A retards the usual acceleration of metamorphosis in tadpoles and in salamander larvae produced by thyroxine [10 11 1] In hyperthyroid rats there is increased utilization of

in a normal person over months or years is far less than that of a group and in fact is relatively characteristic for the individual[196] In thyrotoxicosis the cholesterol level is usually depressed, but this decrease, unless marked, may not become apparent until control of the thyrotoxicosis has returned the cholesterol and lipid level to the individual's normal values For the same reason concentrations within the normal range may occasionally be found in myxedema with eventual depression to the individual s normal as thyroid administration relieves the hypothyroid state[197]

Foldes and Murphy[198] have studied the distribution of cholesterol, cholesterol esters and phospholipid phosphorus in the blood in thyroid disease confirming the earlier work of Boyd and Connell, proving that the alterations occurred primarily in the plasma, with relatively little change in the cell lipid values They noted a constant decrease in the plasma phospholipid phosphorus in hyperthyroidism

In man the role of the thyroid hormone in lipid metabolism appears to be specific since elevation of the basal metabolic rate by dinitrophenol



The Relationship between Blood Cholesterol and Basal Metabolic Rate as Reported in the Literature

The number of observations represented by each point in the figure are

Basal metabolic rat	−40	−30	−20	−10	0	+10	+20	+30	+40	+50	+60	+70	+80
N mbe f b si	4	6	15	15	20	14	21	20	21	16	16	17	12

Fig 8 From Cutting W C Rytand D A and Tainter M L Jour Clin Invest 1934 XIII 547 52

Vitamin C needs are apparently increased by thyroid feeding, and the tissues are depleted of their vitamin C content[illegible] In thyrotoxic patients vitamin C excretion has been found decreased even with a high intake of ascorbic acid thyroidectomy alone serving to cause normal excretory values[illegible]

The relation of thyroid fuction to the metabolism of other vitamins has been studied less extensively As yet these studies have not yielded important physiological or clinical applications[illegible]

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vitamin A [13] as well as increased requirements for vitamin A [14] This has been demonstrated by the production of xerophthalmia in thyroxinized rats on a normal intake of vitamin A There is considerable animal re search tending to show that antecedent use of vitamin A will partly antagonize the calorigenic action of thyroid or thyroxine On the other hand, once hypermetabolism has been produced by either thyroid or thyroxine vitamin A has no antithyroidal effect either in animals [15, 16, 17] or in patients with hyperthyroidism [18]

The development of xerophthalmia in thyroidectomized rabbits ingesting a normal diet [19] ultimately led to the finding that the thyroid hormone is necessary for the conversion of one molecule of carotene into two molecules of vitamin A and for the hepatic storage of vitamin A [0] Thus in cretinism low blood values of vitamin A were unchanged by the administration of carotene [1] Carotenemia is a usual concomitant of human myxedema [2, 3, 4] and is corrected by the administration of thyroid The disturbed metabolism of vitamin A is also reflected in the impaired dark adaptation of hypothyroid patients as vitamin A is essential in the regenerating of the visual purple [5]

The relation of the B vitamins to thyroid function is perhaps simpler than that of vitamin A With hypermetabolism there is an increased need for certain of the B vitamins particularly thiamine pyridoxine panto thenic acid and probably riboflavin Hyperthyroid dogs on a yeast free diet developed anorexia twice as fast as normal dogs on the same diet *The administration of vitamin B concentrate stopped* the weight loss and induced weight gain [6] It was also found that the feeding of thyroid substance to pigeons increased their vitamin B requirements [27] Potent vitamin B concentrate served to prevent weight loss in thyroxinized rats [8]

Further studies of the B complex have indicated the components that are important in relation to thyroid function Drill and Sherwood [9] observed that thiamin stopped weight loss in thyroxinized rats by increasing caloric intake but was ineffective in causing weight gain When however, calcium pantothenate and pyridoxine were added to the thiamin there ensued gain in weight [30] Therefore it may be concluded that thiamin pyridoxine and pantothenic acid are required in increased amounts in experimental thyrotoxicosis The experimental evidence for increased need of riboflavin in hyperthyroidism is not so definitely established In thyroxinized rats there is excessive excretion of riboflavin in the urine [11] and this is associated with decreased tissue content of riboflavin and large losses of body weight

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PART II

THE INTERRELATIONS OF THE THYROID WITH THE OTHER ENDOCRINE GLANDS

The reciprocal relations of the thyroid with other endocrine glands are just as important as its own chemistry and physiology. There can be no adequate understanding of clinical disturbances of thyroid function without knowledge of the factors that control this endocrine equilibrium. The relation with other glands is most importantly manifested in what Salter[1] has termed the *pituitary thyroid axis*, for the pituitary gland plays a dominant part in the control of thyroid development and function.

The Interrelation of the Thyroid and the Anterior Pituitary

The earliest observations on the relation between the pituitary and the thyroid indicated that the integrity of the thyroid affected pituitary function; many years elapsed before it became plain that there was a significant reciprocal interaction between the two glands. Niepce in 1851, in the course of observations on goiter and cretinism, found striking enlargement of the pituitary gland in goitrous cretins. In 1889 Rogowitsch[3] observed great enlargement of the anterior pituitary following *total removal of the thyroid in rabbits and dogs*. Schonemann[4] *confirmed* both these observations when he found that patients or animals with large non-functioning goiters had hypertrophied anterior pituitary glands. Subsequent observations have shown that myxedema and cretinism are regularly associated with significant pituitary enlargement.[5, 6]

The effect of hypophysectomy in producing atrophy and hypofunction of the thyroid was first demonstrated by Ascoli and Legnani[7] in 1911 and confirmed in the following year by Aschner. The acceleration of tadpole metamorphosis by thyroid gland administration first observed by Gudernatsch[9] afforded a new method for studying thyroid function. Hypophysectomy in tadpoles was shown by Adler[1] in 1914

to prevent normal metamorphosis by causing thyroid atrophy Subsequently Smith[11] and, independently, Allen[12] found that extirpation of the pituitary anlage in tadpoles caused failure of the thyroid to develop normally, with secondary arrest of maturation unless thyroid was administered By transplantation experiments with adult pituitaries utilizing normal hypophysectomized, and thyroidless tadpoles Allen[13] clearly demonstrated that the anterior lobe of the pituitary was the portion of the gland concerned with tadpole maturation and that this influence occurred solely through the effect of the pituitary on the thyroid

The dependence of thyroid growth and activity upon normal pituitary function has been observed in amphibia birds and mammals in numerous experiments which are reviewed by Van Dyke[14] Following the demonstration of thyroid hypofunction subsequent to hypophysectomy Smith and Smith[15] showed that the injection of extracts of fresh hypophyses would counteract this decreased function indeed in the normal animal such injections increased thyroid weight and thyroid activity, as measured by increased height of the follicular epithelium in the thyroids of axolotl larvae[16, 1] These experiments led Uhlenhuth and Schwartzbach[16, 17] to postulate the existence of a substance in the anterior pituitary that would cause an increase in thyroid gland activity and in thyroid hormone output Finally in 1930 Crew and Wiesner[18] again using axolotl larvae concluded that extracts of the anterior pituitary contained an activator of the thyroid which was distinct from the growth and gonadotrophic hormones and to which they applied the term thyreotropic hormone

The alterations in thyroid structure and function following hypophysectomy manifest themselves by decreased organ weight and involutional changes characterized by low follicular epithelium and an abundance of deeply staining colloid[19, 0] Parallel with these anatomical changes there occurs evidence of depressed thyroid function The metabolism drops to hypothyroid levels[1] and the blood iodine is similarly decreased However complete myxedema does not develop in animals who have been hypophysectomized or in patients with panhypopituitarism Hypophysectomy depresses but does not completely abolish thyroid function Thus hypophysectomy in the rat does not interfere with conversion of iodide to diiodotyrosine, though there is limitation of the overall conversion of iodide to thyroxine[3] Analyses of rat s gland under these circumstances has shown the presence of normal or even greater than normal amounts of thyroxine in spite of a 50

per cent lowering of the level of hormonal iodine in the blood This finding led Taurog Chaikoff and Bennett [4] to conclude that a lowered concentration of blood thyroxine does not stimulate the thyroid gland into release of stored hormones even when they are present in abundance this release depending upon the action of thyrotrophin Similarly in dogs Bauman Metzger and Marine have shown abundant storage of thyroxine in the form of colloid in the thyroid of hypophysectomized dogs

Hypophysectomy therefore produces a resting colloid rich thyroid histologically and physiologically inactive containing adequate hormone which is not released in normal amounts colloid storage is normal, hormone release is limited or suppressed

The pronounced effects of hypophysectomy upon the thyroid led to a study of the results of transplantation and of the injection of anterior pituitary extracts into animals under various conditions Loeb and Basser [6] and Aron [7] observed that the injection of anterior lobe extracts produced increased cell height in the follicular epithelium of the thyroid of normal animals thus indicating stimulation of thyroidal activity Grant [8] utilizing implants of the anterior pituitary of frogs into amblystoma larvae was able to demonstrate release of the follicular colloid for transcellular migration into the general circulation with eventual complete emptying of the follicles By injection of anterior pituitary powder in the dog Loeser [9] similarly demonstrated depletion of colloid This was associated with increased follicular cell height and papillary infoldings of follicular epithelium such as is seen in thyrotoxicosis

Many other workers have confirmed these results Okkels [3] found an increase in the Golgi apparatus and in the mitochondria following anterior pituitary injections Hertz and Kranes [31] by repeated injections of anterior pituitary extracts in rabbits produced initial thyroid hyperplasia and eventually an involuted gland with atrophy of the epithelium and marked colloid storage Williams [8] observed in living thyroid follicles an increase in the rate and extent of colloid release as a result of injection of anterior pituitary extracts

In man effects similar to complete hypophysectomy were first observed in 1914 by Simmonds [83] who described a clinical syndrome characterized primarily by cachexia with an associated partial failure of thyroid adrenal and gonadal functions this syndrome is now called Simmonds disease In these instances the pituitary has been found atrophic and cicatrized Generalized visceral atrophy also occurs The histology of the thyroid in Simmonds disease varies somewhat but is

to prevent normal metamorphosis by causing thyroid atrophy. Subsequently Smith[11] and, independently, Allen[1] found that extirpation of the pituitary anlage in tadpoles caused failure of the thyroid to develop normally with secondary arrest of maturation unless thyroid was administered. By transplantation experiments with adult pituitaries utilizing normal, hypophysectomized and thyroidless tadpoles, Allen[13] clearly demonstrated that the anterior lobe of the pituitary was the portion of the gland concerned with tadpole maturation and that this influence occurred solely through the effect of the pituitary on the thyroid.

The dependence of thyroid growth and activity upon normal pituitary function has been observed in amphibia, birds, and mammals in numerous experiments which are reviewed by Van Dyke.[14] Following the demonstration of thyroid hypofunction subsequent to hypophysectomy, Smith and Smith[15] showed that the injection of extracts of fresh hypophyses would counteract this decreased function; indeed in the normal animal such injections increased thyroid weight and thyroid activity as measured by increased height of the follicular epithelium in the thyroids of axolotl larvae.[16, 1] These experiments led Uhlenhuth and Schwartzbach[16, 17] to postulate the existence of a substance in the anterior pituitary that would cause an increase in thyroid gland activity and in thyroid hormone output. Finally, in 1930, Crew and Wiesner,[18] again using axolotl larvae, concluded that extracts of the anterior pituitary contained an activator of the thyroid which was distinct from the growth and gonadotrophic hormones and to which they applied the term thyreotropic hormone.

The alterations in thyroid structure and function following hypophysectomy manifest themselves by decreased organ weight and involutional changes characterized by low follicular epithelium and an abundance of deeply staining colloid.[19, 20] Parallel with these anatomical changes there occurs evidence of depressed thyroid function. The metabolism drops to hypothyroid levels[1] and the blood iodine is similarly decreased. However, complete myxedema does not develop in animals who have been hypophysectomized or in patients with panhypopituitarism. Hypophysectomy depresses, but does not completely abolish thyroid function. Thus hypophysectomy in the rat does not interfere with conversion of iodide to diiodotyrosine, though there is limitation of the overall conversion of iodide to thyroxine.[3] Analyses of rat's gland under these circumstances has shown the presence of normal or even greater than normal amounts of thyroxine in spite of a 50

latter substance inhibits a similar synthesis within the gland itself Interestingly thiourea administered by itself will not result in extensive degranulation but iodide plus thiourea produces degranulation similar to that following thyroidectomy presumably through synergistic depression of thyroxine synthesis by the thyroid itself [4]

The restoration of granulation by thyroxine or iodide however is not as effective if their administration is delayed too long after thyroidectomy Similarly Severinghaus [46] has shown that in rats thyroidectomized at birth irreversible changes occur in the pituitary there is a permanent absence of acidophil and basophil cells

The rat is unique in the clarity with which a particular cell type can be related to the elaboration of thyrotrophin In the cockerel data are not conclusive and suggest if anything that acidophils are the likely source of thyrotrophin [4] The guinea pig is also different in that no obvious counterpart to the thyroidectomy cells of the rat appears after profound depression of the thyroid D'Angelo [4b] however on the basis of thyrotrophin assays of the blood and pituitary in this animal concludes that thyrotrophin is produced by the basophils

Thyrotrophin

The Thyrotrophic Hormone The unitary nature of the thyrotrophic hormone as it affects the structure and function of the thyroid has not yet been clearly established nor is there always a regularly demonstrable parallelism between the degree of morphological change and functional alteration Heyl and Laqueur [47] found that various pituitary extracts selectively increased thyroid weight or produced hyperplasia Billingsley [48] also concluded that thyrotrophin might have dual effects — one influencing the secretion of the thyroid hormone the other acting upon the gland structure Chemically however the hormone has been characterized as a protein relatively low in molecular weight and probably containing a carbohydrate grouping [49] Though it has not yet been isolated as a pure substance simple procedures for its preparation in highly purified form are now available [a] Previous conclusions about the nature of the hormone may well have been confused by the presence of contaminating materials particularly gonadotrophic substances which are difficult to separate from thyrotrophin Prolactin and the growth hormones are more readily separable

The effects of thyrotrophin on thyroid morphology consist of an increase in the height of the follicular cells hypertrophy and hyperplasia

always consistent with marked hypofunction. Means and his associates[34] found a slightly fibrosed small gland containing sparse follicles with low epithelium and little colloid. Farquharson[3] also found a small thyroid with great reduction in the number of follicles and extremely thin cells in most cases, but in one instance he noted a picture suggestive of early primary myxedema with small irregular bunches of follicles and marked fibrosis.

On the other hand, hyperpituitarism, as exemplified in man by acromegaly and giantism, is usually associated with marked enlargement of the thyroid gland. Changes in the thyroid have been described by Cushing and Davidoff[36] and by Atkinson[37] and are essentially those of colloid hypertrophy, frequently with adenomatous formation. Elevation of the basal metabolic rate is not uncommon,[38] but instances of true hyperthyroidism rarely occur.

The production of hypophyseal enlargement by thyroidectomy occurs through unknown neural mechanisms according to Salter,[1] but is associated with increased concentration of thyrotrophin in the blood. Zeckwer[39] found large amounts of thyrotrophin in the pituitaries of cretinous rats. The histological changes occurring in the anterior pituitary following thyroidectomy in man are characterized by an increase in the number, size, and degree of vacuolization of the basophilic cells and a decrease in the number and size of the eosinophilic cells.[40] In rats, inhibition of thyroid function by antithyroidal goitrogens such as Brassica seed and soy bean diets[41, 42, 43] leads to similar changes associated with a definite reduction in the thyrotrophin concentration in the anterior pituitary.

Thyroidectomy in rats results in striking changes in both types of chromaffin cells of the pituitary. The basophil ('thyroidectomy') cells are greatly increased in number and size, while the acidophil or eosinophil cells lose their acidophilic granules and come to resemble the chromophobe cells. The degranulation of the acidophil cells occurs only with extreme thyroxine deficiency, while the hypertrophy of the basophil cells occurs only in states coinciding with increased production of thyrotrophin. Thus Griesbach and Purves[44] have concluded that the basophil cells are the source of thyrotrophin. Acidophilic degranulation can be quantitatively prevented by throxine administration in amounts as little as 0.25 micrograms per 100 grams of rat daily and has been found a sensitive indicator of the presence of thyroxine *in vivo*. Iodide as well as thyroxine will prevent acidophilic degranulation following thyroidectomy, and this protective action has been ascribed to extrathyroidal thyroxine synthesis. This synthesis is inhibited by thiourea just as the

The direct effect of thyrotrophin on the thyroid gland has been assayed by measuring the increase in thyroid weight in acinar cell height, or in the intracellular colloid droplets It has also been assayed chemically by determining the decrease in thyroid iodine content

Borrell[61] and Griesbach and Purves[6] have found a specific parallelism between thyrotrophin stimulation and increased cell height in the thyroid of young guinea pigs The findings of Rowlands and Parks[6] that thyrotrophin quantitatively increases the thyroid weight of the newly hatched chick have been confirmed by Smelser[63] and Adams[64] this increased weight may be used as a sensitive and reliable method of thyrotrophin assay DeRobertis[6] and later Dvoskin[67] have described and utilized as an assay method the production of intracellular colloid droplets following thyrotrophin stimulation This method is sensitive and permits quantitation in as little as 2 0 cc of human blood but its specificity is open to question since these droplets can form in vitro in the absence of added thyrotrophin

The assay of thyrotrophin by measurement of the decrease in thyroid iodine content in young cockerels as proposed by Piotrowski and his associates[6 b] requires careful selection of animals and season of the year as well as measurement of total iodine content of the thyroid gland to produce assays with a standard error of 25 per cent

The method of Junkmann and Schoeller[66] has gained the widest acceptance for measuring thyrotrophin activity in units A unit of activity is defined as that amount of hormone which when injected daily for three days causes recognizable hypertrophy of the epithelium and disappearance of colloid in the thyroids of guinea pigs weighing 100 to 150 grams (Fig 9–15)

The assay of thyrotrophin in patients with disorders of the thyroid has been attempted by many investigators It has been particularly studied in Simmonds disease[1] acromegaly[68] myxedema and hyperthyroidism[67 69 0 71 7 3]—both in the urine and in the blood Most of these studies have yielded contradictory data because the assay methods utilized have varied and have not been adequate Thyrotrophin as it occurs in the hypophysis has not been conclusively demonstrated in the blood and urine of human subjects in spite of the fact that thyrotrophin added in tracer amounts can be satisfactorily recovered from these media by chemical methods[74]

D Angelo and his co workers[74] have investigated thyrotrophic activity in the blood of patients suffering from a variety of endocrine disorders They have used the starved tadpole for bioassay of thyro-

of the epithelium such as is seen in exophthalmic goiter, vacuolization and eventual resorption of the colloid, and increase in vascularity and gland size [51, 1] Papillary infoldings of the epithelium with colloid absorption have been demonstrated as early as 2 hours after intraperitoneal injection of thyrotrophin into guinea pigs By the end of 24 hours the colloid space has been found decreased by 50 per cent These changes are reversible with complete return to the normal picture 7 days after injections of thyrotrophin have been discontinued [51] On the other hand Loeser [3] and Elmer [54] by continuous and increasing doses of thyrotrophin produced chronic thyrotoxicosis which was eventually fatal

Chemically, thyrotrophin has important effects on the hormonal and iodine content of the thyroid gland and of the blood Following thyrotrophin stimulation the thyroid shows a striking decrease in iodine content [3, 55] especially in the thyroxine like fraction [6, 7] while the hormonal iodine concentration in the blood increases This is analogous to the situation occurring in clinical thyrotoxicosis — low hormonal iodine content of the gland with elevated levels of hormonal iodine in the blood Thyrotrophin not only increases the level of hormonal iodine in the blood but according to Chaikoff and his associates [60] it also greatly augments the rate of conversion of inorganic iodine into the protein bound iodine of the blood In addition as previously indicated with regard to the effects of hypophysectomy [4] the rate at which thyroid hormone is released into the circulation is also controlled by thyrotrophin Closs Loeb and MacKay [58] have shown that thyrotrophic stimulation may reduce the iodine content of the thyroid by over 90 per cent producing a gland that has scarcely any pharmacological activity and only traces of thyroxine

Thyrotrophin is thus seen as the indispensable factor that controls the rate and amount of thyroid hormone production and its release by the gland secondarily it has important effects on blood iodine levels

Assay of Thyrotrophin Thyrotrophin has been assayed both by measuring the secondary effects resulting from the increased activity of the thyrotrophin stimulated thyroid gland and by quantitating its direct effect on the histology and secretory activity of the thyroid Animal species of appropriate sensitivity must be utilized and for this purpose the tadpole guinea pig or chick have been found most responsive The metamorphosis of amphibian larvae such as the tadpole has largely served as the basis for measurement of the indirect effect of the thyroid gland stimulated by thyrotrophin [63] The tadpole possesses the advantages of convenience and sensitivity but its specificity is not as clearly established as that of the guinea pig and chick

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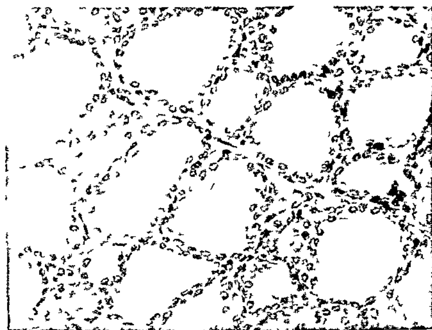


Fig 9 Thyroidea from guinea pig Normal animal Cell height $8.3 \pm 0.15\mu$ The follicles well filled with colloid Few vacuoles



Fig 10 Thyroidea from guinea pig Normal animal Clear border line between follicle cells and colloid

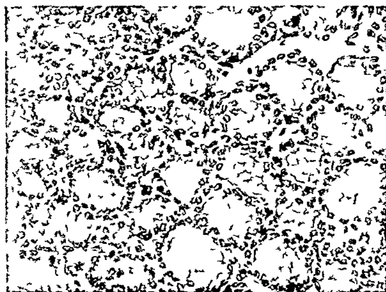


Fig 11 Thyroidea from guinea pig killed hours after a single injection of MsU of thyrotropic hormone Cell height $8.8 \pm 0.11\,\mu$ Great vacuolization of the colloid

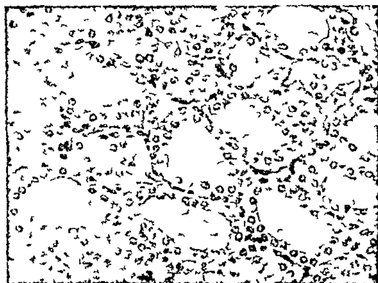


Fig 12 Thyroidea from guinea pig killed 12 hours after a single injection of 2 MsU of thyrotropic hormone Cell height $10.2 \pm 0.10\,\mu$

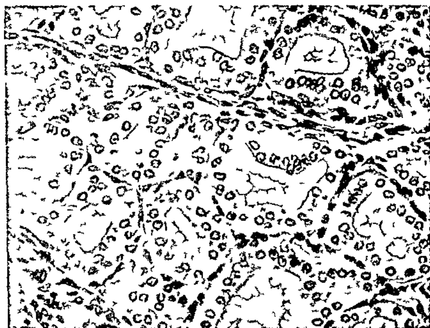


Fig 13 Thyroidea from guinea pig killed after 4 daily injections of 2 MsE of thyrotropic hormone Cell height $14\ 1 \pm 0\ 14\ \mu$ In places the follicle walls bulge into the lumen The nuclei are localized in parts of the cell which are directed toward the lumen

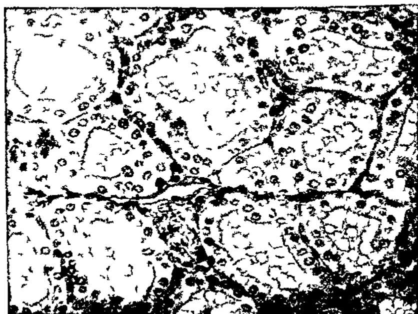


Fig 14 Thyroidea from guinea pig killed after 8 daily injections of 2 MsE of thyrotropic hormone Cell height $14\ 4 \pm 0\ 12\ \mu$ Great vacuolization of the colloid



Fig 15 Thyroidea from guinea pig which received 2 MsL of thyrotropic hormone daily during 8 days Some of the follicle cells cut very obliquely All illustrations in this section are from Borell U On the transport route of the thyrotropic hormone the occurrence of the latter in different parts of the brain and its effect on the thyroidea Acta Med Scand 1945 Supplement clxi 1 2 7

trophin since complete starvation induces thyroid atrophy and meta morphic stasis in this animal This method is sensitive enough to measure the presumably low concentrations of thyrotrophin in human body fluids The studies of this group indicate that there is probably an increase in thyrotrophin in hyperpituitarism and a decrease in hypo pituitarism *The great majority of hypothyroid individuals did not show* excessive titers of thyrotrophin conversely in hyperthyroidism thyro trophin levels were usually normal D Angelo and his associates there fore postulate that the hyperplasia and increased activity of the thyroid gland in thyrotoxicosis cannot be attributed to an abnormal concentra tion of thyrotrophin in the blood In addition they found ophthalmo pathic hyperthyroidism present when thyrotrophin was either absent normal or excessively high high levels found in acromegaly and in occasional cases of primary myxedema were not associated with exophthalmos

Thyrotrophin Iodine and Thyroid Hormone Early investigations by Loeb and his co workers[7 78] demonstrated that the administration of thyroid substance partially inhibited the thyroid hyperplasia caused by

thyrotrophin. This finding was confirmed for thyroxine by Aron and his associates[76] and by Loeser and Thompson.[78, 79] The latter investigators also found, as had Kuschinsky[80] before them, that large doses of iodine led to increased thyrotrophin content of the pituitary, whereas small doses depressed its production.

Kuschinsky[80] clearly showed the equilibratory relations between the thyroid hormone and thyrotrophin by assaying in guinea pigs the pituitary glands of rats that had received thyroxine. The cellular hyperplasia of the thyroid produced by the implantation of pituitaries from normal rats failed to occur when pituitaries from thyroxinized rats were used. Adams and Jensen[81] found a 90 per cent decrease in the thyrotrophic content of anterior pituitaries of thyroxinized mice. Cortell and Rawson[6] observed that thyroxine depressed the response of the animal's thyroid gland to thyrotrophin both in normal and in hypophysectomized animals. More recently Purves and Griesbach,[6] utilizing the same method as Kuschinsky,[80] concluded that thyroid administration depressed the thyrotrophic activity of the rat's pituitary by over 95 per cent. In an over-all application of this work as well as of his own research Marine[84] concluded that in the normal animal thyrotrophin is the sole cause of increased thyroidal activity, and that inadequate supply of environmental iodine leads to goiter through thyrotrophic stimulation of the thyroid.

The effect of iodine upon the reciprocal relation between the pituitary and the thyroid has been studied in the living organism, in tissue slices and in the test tube. Siebert and Thurston,[8] Friedgood,[86] and Elmer[4] all found that iodides inhibited an established thyrotrophic effect. Anderson and Evans found that potassium iodide inhibited the metabolic effect of thyrotrophin without interfering with the changes in the thyroid itself, possibly accomplishing this effect by preventing the discharge of thyroxine from the gland.

In vitro experiments by Seidlin[88] *have suggested that thyroid* tissue in some way inactivated or removed thyrotrophic hormones from surrounding solutions. Galli Mainini[89] similarly found an in vitro inhibition of thyrotrophin when it was placed in contact with thyroglobulin. Rawson and his co-workers[90] likewise observed that normal thyroid tissue removed the thyrotrophic effect of pituitary extracts, and again that thyroid slices from thyrotoxic patients inactivated twice as much thyrotrophin as normal thyroid.[91] Finally Albert, Rawson and Merrill[2] added elemental iodine to pituitary extract in the test tube and abolished thyrotrophic activity in proportion to the amount of iodine added; with enough iodine most of the thyrotrophin was inactivated. Junqueira[93]

has reported a similar inhibition of thyrotrophin by iodide added to thyroid fragments in vitro

Metabolic Effect of Thyrotrophin The marked histological changes produced in the thyroid gland by thyrotrophin are indicative of increased secretion of thyroid hormone This in fact is borne out by studies on experimental animals Siebert and Smith[94] Anderson and Collip[2] and others[95] have shown that thyrotrophin elevates the metabolic rate for about 2 weeks and that after this period there ensues a return to normal or depressed values unless increased amounts of thyrotrophin are administered[3,4] This metabolic effect does not occur in the absence of the thyroid gland[97,98] The hypermetabolism is correlated with decreased thyroxine iodine content of the gland and marked increase in organically bound blood iodine suggesting that the rise in oxygen consumption is due to release of increased amounts of thyroid hormone[19]

The transient effects of moderate doses of thyrotrophin upon the thyroid histology and metabolic rate led Collip[11] to investigate the possible existence of anti hormones as an explanation of the refractory state Whether anti hormones as such develop or whether the phenomenon may be explained on the basis of antibodies developed to react against the protein portion of thyrotrophin as suggested by Werner[101] is at present unsettled Since large doses will produce permanently hyper thyroid states the explanation of this relative refractoriness may be of the nature of tachyphylaxis — i e the development of tolerance to repeated administration such as is seen with other drugs and biological agents

Measurement of the oxygen consumption of thyroid tissue itself has been utilized in further studies of the physiological effects of thyrotrophin The technique of Warburg for measurement of tissue oxygen consumption (QO) has been utilized by some investigators The metabolism of thyroid slices from animals previously injected with thyrotrophin or the addition of thyrotrophin to the medium in which thyroid slices from normal untreated animals are suspended have provided alternative approaches to this study Paal[1] Canzanelli and Rapport[103] and VanderLaan and his co workers[104] have utilized the former technique whereas Anderson and Alt[105] and Galli Mainini[6] have used normal thyroids bathed in a thyrotrophic containing medium In both groups of experiments the oxygen consumption was found increased but this increase was greater in the pre treated animals Borell[91] has carefully reviewed and restudied the findings in the thyrotrophin treated animal and has clearly shown that within several hours after such

thyrotrophin This finding was confirmed for thyroxine by Aron and his associates[7] and by Loeser and Thompson[78, 79] The latter investigators also found, as had Kuschinsky[80] before them, that large doses of iodine led to increased thyrotrophin content of the pituitary, whereas small doses depressed its production

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euthyroid hyperthyroid or acromegalic They observed maximum effects from thyrotrophin during the first 24 hours in thyrotoxic patients and not until 48 hours later in euthyroid subjects

Thyrotrophin and Exophthalmos

Thyrotrophin is significantly related to the production of exophthalmos in the experimental animal Gley [108] first noticed the occurrence of exophthalmos following thyroidectomy in young rabbits Zimmerman [109] similarly noted exophthalmos following thyroidectomy in patients with hyperthyroidism Loeb and Bassett [8] Schockaert [110, 111] and Loeb and Friedman [11] first demonstrated that exophthalmos frequently ensued following injection of anterior pituitary extracts in guinea pigs and ducks Schockaert for instance found that 14 out of 15 ducks injected with a crude extract of the anterior hypophysis developed exophthalmos after 3 weeks of treatment

Marine and his associates [113, 114, 115] later discovered that the goitrogen methyl cyanide frequently produced exophthalmos in rabbits that this exophthalmos was proportional to goitrogenesis that it did not occur in resistant rabbits which failed to develop thyroid hyperplasia and that this resistance could be completely abolished by thyroidectomy Thyroidectomy in fact increased any existing exophthalmos Iodine administration prevented exophthalmos in rabbits with an intact thyroid but administered thyroid did not abolish an existent exophthalmos Marine felt that cyanide produced thyroid hyperplasia by stimulation of the anterior pituitary and then demonstrated that extracts of this gland would produce exophthalmos in normal and in thyroidectomized guinea pigs in the former group no exophthalmos developed until the thyroid became hyperplastic Furthermore Marine [116, 117] found that castration inhibited the exophthalmos produced by the anterior pituitary while testosterone accelerated its appearance

Smelser [118, 119, 120, 121] has elucidated the subject further He found that injections of anterior pituitary extracts produced hyperfunctioning goiters in guinea pigs but no significant exophthalmos except in thyroidectomized guinea pigs Under these conditions marked exophthalmos developed after 2 to 3 weeks of treatment The development of this exophthalmos was not prevented by excision of the cervical sympathetic ganglion and persisted after death The orbital contents in these animals were increased in weight and size primarily because of an increase in the

treatment the removed thyroid will have an elevated QO_2 or oxygen consumption which will be maintained under the influence of daily injections for about 7 weeks when a great decline occurs with the development of very low values for QO_2

Another important metabolic effect of thyrotrophin is alteration of the glycogen content of the liver Continued injections of thyrotrophin will entirely deplete the liver of its glycogen, [1 61] provided the thyroid gland is present but will have no effect in thyroidectomized animals This glycogenolytic effect may, therefore be viewed as a secondary action of thyrotrophin mediated entirely by the release of thyroxine

The relation of this physiological and experimental data to clinical states is far from clear Thompson and his co-workers [106] have been able to elevate transiently the metabolic rate of normal and goitrous patients through the use of extracts of the anterior pituitary and at the same time to produce thyrotoxic symptoms This work is suggestive but needs confirmation On the other hand pathological studies have failed to disclose alterations in the histology of the anterior pituitary in thyrotoxicosis in man [107]

Though the relation of clinical hyperthyroidism to thyrotrophin is unknown there has been some clarification of the normal role of thyrotrophin in human thyroid physiology Many investigators have administered thyrotrophin in a relatively impure form to human subjects in various states of thyroid function, and its effects have been studied by tracer amounts of radioactive iodine Stanley and Astwood [10 a] found a latent period of 8 or more hours before there was a detectable increase in thyroid activity as measured by increased organic binding of iodine by the thyroid and by its increased capacity to concentrate the iodide ion i e iodine uptake These two processes were demonstrated to be independent since increased uptake or iodine concentrating capacity occurred when organic binding was inhibited by mercaptoimidazole Goldsmith and his associates [107b] similarly found that in thyrotoxic patients thyrotrophin increased the rate of release of thyroid hormone from the thyroid hormone stores in spite of the inhibition of iodide accumulation in the thyroid by mercaptoimidazole The total amount of hormone release was naturally smaller in the thyrotoxic gland than in the euthyroid gland since the hyperthyroid gland is already depleted of its hormone stores but the rate of release is made even greater by thyrotrophin Beeler and his associates [107] also noted that thyrotrophin increased the levels of both protein bound radioactive iodine (PBI [131]) and ordinary protein bound iodine in the blood of patients who were

depended on the dosage He found no difference between normal and thyroidectomized animals ascribing the differences reported by other observers to the greater weight loss in the intact animal In the animals used in these experiments the exophthalmos was found to be due largely to increased water content of the orbit

Rundle and Pochin [1] also studied the manner and degree of exophthalmos in thyrotoxic patients at post mortem examination By chemical rather than histological techniques they were able to demonstrate that the increased bulk of the orbit which occurs in thyrotoxic patients was mainly due to increased fat content in the orbital structures even in the presence of emaciation

This increase of fat was relatively greatest in the eye muscles particularly in the levator palpebrae superioris though the increase in the general orbital fibro fatty tissue was responsible for most of the increase in bulk Rundle and Pochin s conclusions were based largely on the amount of ether soluble material extracted from these orbits and it is important to point out particularly in view of Smelser s conclusions with histological techniques that no attempt was made to analyze other materials such as collagen or nuclear material which may have increased *pari passu* with the fat

In the guinea pig Smelser [1,0] found that anterior pituitary exophthalmos was unaffected by the coincident administration of sodium iodide and that thyroxin reduced the incidence of exophthalmos Diiodotyrosine had no effect on the orbital contents in the normal or exophthalmic pigs whereas thyroxine caused a marked enophthalmos by reducing the contents of the orbit Exophthalmos however could be produced in hyperthyroid pigs but in lesser degree than in thyroidectomized animals

Albert [1,6] has investigated the problem in *Fundulus* the common Atlantic minnow In this fish striking proptosis was regularly produced by injection of adequate amounts of anterior pituitary extracts The active principle of these extracts was shown to be closely associated with thyrotrophin since all preparations that induced exophthalmos also produced thyroid hyperplasia in hypophysectomized frogs and turtles conversely anterior pituitary preparations that did not produce exophthalmos had no thyroid stimulating action Albert labeled this fraction the exophthalmic factor and further noted that exophthalmos preceded thyroid hypertrophy and hyperplasia by at least 1 hours The mechanism of the exophthalmos in *Fundulus* consisted of increased intra orbital pressure due to free retrobulbar fluid and edema of the areolar and fat tissue within the orbit This investigator is critical of the general belief that

fatty connective tissue the dorsal lacrimal gland, and the extra ocular muscles The retrobulbar tissues contained a stainable infiltrate showing granules droplets — probably lipoid in nature — and round cells penetrating between the fat cells and into the connective tissue The extra ocular muscles showed irregular clumps of round cells and the same type of edematous infiltration as was seen in the retrobulbar tissues In addition the orbital tissues showed considerable numbers of wandering cells

Paulson[1] confirmed many of Smelser s observations finding however that exophthalmos developed readily in guinea pigs with intact thyroid glands although not in every animal and never to the same degree as in the thyroidectomized pig The orbital tissues of these animals contained excessive water in the fat connective tissues and muscles, as well as cellular infiltration

Dobyns[1 3] has correlated the orbital changes caused by thyrotrophin with generalized tissue changes He too found that the development of exophthalmos was facilitated by thyroidectomy but that exophthalmos was induced readily in animals with intact thyroid glands when they were given adequate doses of thyrotrophin He observed large numbers of mononuclear and polymorphonuclear cells in the connective tissue throughout the body following thyrotrophin injection With these cells were associated varying edema and fibroblastic proliferation The fat depots including the orbit of the animal showed many phagocytic cells both polymorphonuclear and mononuclear, along with fibroblasts containing tiny fat droplets Dobyns inferred that the macrophages turned into fibroblasts which in turn laid down connective tissue There was edema in the interstices of the connective tissue and in the orbital fat as well as separation of the muscle fibers apparently by edema fluid

Smelser[115] has compared the orbital changes of patients dying with thyrotoxicosis with what has been found in exophthalmos produced experimentally by injections of anterior pituitary extract In man he found an edematous infiltrate and wandering cells in the fat connective tissue, and muscles The infiltrate was seen as a stainable substance which penetrated between the collagen fibers of the connective tissues and at times between the fat cells, resembling closely the material found in the guinea pigs The wandering cells appeared as in the guinea pigs, and the muscle changes were also similar consisting of edema and round cell infiltration

Pochin[1 4] utilizing objective ocular measurements demonstrated that exophthalmos could be produced readily in growing guinea pigs by injection of anterior pituitary extract and that the degree of exophthalmos

depended on the dosage He found no difference between normal and thyroidectomized animals ascribing the differences reported by other observers to the greater weight loss in the intact animal In the animals used in these experiments the exophthalmos was found to be due largely to increased water content of the orbit

Rundle and Pochin[1] also studied the manner and degree of exophthalmos in thyrotoxic patients at post mortem examination By chemical rather than histological techniques they were able to demonstrate that the increased bulk of the orbit which occurs in thyrotoxic patients was mainly due to increased fat content in the orbital structures even in the presence of emaciation

This increase of fat was relatively greatest in the eye muscles particularly in the levator palpebrae superioris though the increase in the general orbital fibro fatty tissue was responsible for most of the increase in bulk Rundle and Pochin s conclusions were based largely on the amount of ether soluble material extracted from these orbits and it is important to point out particularly in view of Smelser s conclusions with histological techniques that no attempt was made to analyze other materials such as collagen or nuclear material which may have increased *pari passu* with the fat

In the guinea pig Smelser[10] found that anterior pituitary exophthalmos was unaffected by the coincident administration of sodium iodide and that thyroxin reduced the incidence of exophthalmos Diiodotyrosine had no effect on the orbital contents in the normal or exophthalmic pigs whereas thyroxine caused a marked enophthalmos by reducing the contents of the orbit Exophthalmos however could be produced in hyperthyroid pigs but in lesser degree than in thyroidectomized animals

Albert[16] has investigated the problem in *Fundulus* the common Atlantic minnow In this fish striking proptosis was regularly produced by injection of adequate amounts of anterior pituitary extracts The active principle of these extracts was shown to be closely associated with thyrotrophin since all preparations that induced exophthalmos also produced thyroid hyperplasia in hypophysectomized frogs and turtles conversely anterior pituitary preparations that did not produce exophthalmos had no thyroid stimulating action Albert labeled this fraction the exophthalmic factor and further noted that exophthalmos preceded thyroid hypertrophy and hyperplasia by at least 12 hours The mechanism of the exophthalmos in *Fundulus* consisted of increased intra orbital pressure due to free retrobulbar fluid and edema of the areolar and fat tissue within the orbit This investigator is critical of the general belief that

thyrotrophin causes exophthalmos because of the relative impurity of the extracts thus far employed by others He points out that his own work has shown an intimate relation between thyrotrophin and the exophthalmic factor since both are located in the same mixture of pituitary proteins and may prove to be identical Dobyns and Steelman,[126] however, after studying a variety of pituitary extracts, were able to separate an exophthalmos producing substance from thyrotrophin, utilizing the production of exophthalmos in the *Fundulus* as an assay method Their separations were fairly complete in that all of the exophthalmogenic factor could be removed from thyrotrophin, and most of the thyrotrophin could be removed from the exophthalmos producing factor

The Regulation of Thyrotrophic Activity

Thyrotrophin acts directly on the thyroid cell through a humoral mechanism which does not require the mediation of nervous tissue as was first shown in vitro by Eitel Krebs, and Loeser[127] Marine and Rosen[128] similarly demonstrated stimulation of thyroid transplants by thyrotrophin Krayer[129] Uotila[130] and Loewe, Ivy, and Brock[131] have conclusively shown that the cervical sympathetic chain is not essential for the effect thyrotrophin has on the thyroid Uotila[132] has further shown that the reciprocal relation between thyroxine and thyrotrophin is independent of hypothalamic stimuli passing through the pituitary stalk The anterior pituitary of animals shows similar changes following thyroxine administration whether the stalk is intact or partially or completely transected Thyrotrophic function is basically regulated by variations in the thyroxine level of the blood Cervical sympathectomy may have a minor and temporary role in decreasing thyrotrophic function, but no permanent effect ensues Similarly under the stress of cold the pituitary stalk may transmit stimuli from the hypothalamus with modification of the thyroxine thyrotrophin balance Jacobsohn and Westman[133] have contrasted the relative independence from the hypothalamus of thyrotrophin with the dependence of the gonadotrophic hormone upon the hypophyseal-hypothalamic relationship

Greer[133a] however, on the basis of carefully placed electrolytic lesions in the hypothalamus of rats and of intra-ocular transplantation of the pituitary in hypophysectomized mice, has suggested that thyrotrophin consists of at least two factors—a 'growth' factor and a 'metabolic' factor The growth factor regulates thyroid cell height and gros s

thyroid size and depends on the integrity of certain areas of the hypothalamus which have some manner of direct communication with the anterior pituitary The metabolic factor is independent of the hypothalamus enabling the thyroid to concentrate and bind iodine

It is entirely probable that thyrotrophin can pass directly into the blood stream Westman and Jacobsohn[134] have demonstrated this likelihood with regard to gonadotrophin Borell[81] has concluded that the thyrotrophic hormone is transported by way of the stalk of the hypophysis to the tuber cinereum whence it reaches the choroid plexus probably by way of the third ventricle Alternate routes of transport undoubtedly exist

THE INTERRELATION OF THE THYROID AND THE NEURO HYPOPHYSIS

The role of the thyroid hormone in water exchange has been discussed in Part I The production of diuresis in normal animals by the administration of anterior hypophyseal extracts containing thyrotrophin led several investigators[11, 136] to conclude that the diuretic action of the anterior hypophysis was mediated through the thyroid gland In an extensive and meticulous series of investigations on the neuro hormonal control of water balance Fisher Ingram and Ranson[137] restudied this problem in cats with experimental diabetes insipidus They found a variable effect from thyroidectomy some animals developed a 50 per cent reduction in the level of fluid exchange though others showed no appreciable reduction but in no case did the water exchange fall to *normal The administration of thyroid extract in doses of 1 gram daily* restored the fluid exchange to its level before thyroidectomy

These authors also studied the effect of thyroid administration on normal cats and on cats with diabetes insipidus The dosage of thyroid used was very large varying from 1 to 4 grams daily Very little increase in water exchange occurred even after unphysiological doses over a period of several weeks In the cats with diabetes insipidus there was marked increase in the fluid exchange with doses of thyroid that had little effect on the normal animals The greater sensitivity to thyroid was ascribed to a deficiency of the antidiuretic hormone of the neuro hypophysis with exaggeration of the diuretic tendency by the administra*tion of thyroid*

Heinbecker and his associates[13] have clarified further the role of the thyroid in diabetes insipidus by showing that in dogs the pars distalis

of the anterior hypophysis must be left intact to produce permanent maximal diabetes insipidus following the destruction or denervation of the neuro hypophysis Removal of the pars distalis shortens and ameliorates the extent of the diabetes insipidus by causing secondary atrophy of the thyroid and adrenal cortex with abolition of their diuretic activity Their work suggests the possibility that thyrotrophin is elaborated in the pars distalis of the anterior pituitary

Total thyroidectomy has been utilized in human cases of diabetes insipidus with variable results Findley and Heinbecker [139] and Ferro Luzzi [140] found no improvement following the operation, whereas Blotner and Cutler [141] observed great improvement in 2 out of 3 patients who were subjected to total thyroidectomy

Thyroid-Parathyroid Interrelations

There is little or no evidence indicating any direct relation between the thyroid and parathyroid glands in the endocrine system of normal individuals The relative roles of these two glands in the regulation of mineral metabolism has been discussed in Part I Various authors however have found a parallelism in the response of the thyroid and para thyroid glands to various hormones Zondek [14] has shown that there is simultaneous stimulation of the thyrotrophic and parathyrotrophic functions of the pituitary by prolonged injections of estrogen Nathanson and his associates [143] found that injections of testosterone propionate in rats increased the proliferative activity of the thyroid and parathyroid glands They ascribed this action to stimulation of the anterior hypophysis Finally Blumenthal and Loeb [144] have noted that administration of anterior hypophyseal extracts caused increased mitotic activity and cell proliferation in both the thyroid and parathyroid glands and that underfeeding as well as the administration of thyroid substance resulted in a marked decrease in mitotic activity in both the thyroid and para thyroid glands The cause of this parallel response remains unexplained particularly in view of the disputed existence of a parathyrotrophic hormone

Interrelations of the Thyroid and Adrenals

Though it appears that the thyroid and adrenals have a significant relationship the exact endocrine balance and the mechanisms involved have not been clarified Marine has maintained that an antagonistic rela-

tion exists between the two glands he bases his view on the finding of increased metabolism following bilateral adrenalectomy and on the persistent elevation of metabolism that follows sublethal injury to the adrenals[14, 148] The effect of adrenalectomy in raising the metabolism of experimental animals has been confirmed by Davis and Hastings[147] It must be that the increased metabolism following reduced function of the adrenal cortex is mediated through the thyroid gland for it does not occur in athyreotic animals[14] Adrenal hypertrophy frequently occurs in hyperthyroidism[149] and the administration of thyroid produces adrenal cortical enlargement[13, 150] On the other hand Bock[151] found that adrenal cortical extract behaves synergistically with thyroxin in the acceleration of tadpole and axolotl metamorphosis

Baumann and Marine[3] in more recent studies produced involution of the adrenal cortex in rats by thiouracil ingestion and considered this regression as a compensatory reaction to loss of thyroid secretion The action of the thyroid in causing adrenal cortical hypertrophy is mediated through the hypophysis since thyroxin will not induce hypertrophy of the adrenal cortex in hypophysectomized animals[1, 9, 3, 3, 154] Furthermore thyrotrophin itself will produce adrenal cortical hypertrophy[1, 158] which can be prevented by iodide[1, 7]

The availability of adrenocortical steroids and of corticotrophin has restimulated interest in the relations between the thyroid and the adrenal glands This relationship has been investigated in both man and experimental animals by determining the effect of cortisone or corticotrophin representing respectively exogenous and endogenous adrenocortical steroids upon thyroidal metabolism as measured by oxygen consumption levels of protein bound iodine radioactive iodine uptake the renal plasma clearance of radioactive iodine and particularly in animals quantitation of the amount of thyrotrophin in the anterior pituitary or in the blood

Cortisone in doses of 100 mg daily quite regularly inhibits the iodine accumulating function of the thyroid and usually produces an increase in the clearance of I^{131} by the renal plasma according to Berson and Yalow[3] This effect of cortisone is persistent so long as adequate amounts are administered but disappears within a few days after its omission The depressed uptake of I^{131} represents a true decrease in thyroid function rather than a lessened availability of iodine from increased renal excretion for the thyroidal plasma I^{131} clearance was clearly decreased Thus according to these authors the capacity of the thyroid cells to clear plasma of its I^{131} content is strikingly diminished by cortisone

Cortisone in daily doses of 400 to 500 mg markedly depresses the uptake of I^{131} in euthyroid individuals and, when the cortisone is given intramuscularly causes a depression that may persist for weeks because of the depot' effect of intramuscularly administered cortisone Concomitantly there is usually a significant decrease in the level of protein bound iodine of the blood and an increase in the serum cholesterol These laboratory signs of thyroidal depression do not occur in patients with thyrotoxicosis who are given massive doses of cortisone, according to Fredrickson Forsham and Thorn[1 b]

The mechanism responsible for the inhibition or depression of I^{131} uptake by adrenocortical steroids is not entirely clear Albert and his co-workers[1] properly point out that thyroid function should be defined as the amount of hormone secreted by the gland in a unit of time that is the hormonal secretion rate This is not a feasible measurement The rate of biologic decay of thyroidal I^{131} however, may be utilized as an indirect measurement of the rate of hormone secretion and as a more sensitive criterion of thyroidal function than I^{131} accumulation Albert[1] found that cortisone and corticotrophin did not depress the I^{131} secretion rate of the rat s thyroid, even though they did depress uptake as in man He concludes therefore that the depressed uptake cannot be due to inhibition of thyrotrophin since both uptake and discharge of I^{131} are strikingly lowered when thyrotrophin is absent or inhibited Halmi and Barker[1 d] indeed found that cortisone administered to rats produced histological evidence in both pituitary and thyroid glands of an increased rate of thyrotrophin release from the pituitary D Angelo and his associates[1] came to similar conclusions Halmi[1 f] in addition has demonstrated that cortisone treated rats have an unimpaired capacity to concentrate iodide despite a defective I^{131} uptake

From the work of Albert and Halmi it may be concluded that cortisone does not inhibit thyrotrophin and does not prevent access of iodide to the thyroid cell Cortisone must therefore depress uptake either (1) by affecting the extrathyroidal metabolism of iodide through increasing renal excretion or iodide space or (2) by partially inhibiting organic binding of iodine in the thyroid Ingbar and Chandler[1 7e] found that the rate of clearance of plasma iodide by the thyroid glands of hypophysectomized rats was unaltered by cortisone even when thyrotrophin was administered The decreased uptake of I^{131} in these animals resulted entirely from a marked increase in the renal clearance of iodide In this regard they found that desoxycorticosterone was antagonistic to cortisone diminishing iodide clearance by the kidneys

In man Zingg and Perry [3] noted that desoxycorticosterone in daily doses of 10 mg for 3 days depressed the uptake of I^{131} as much as cortisone in a dose of 150 to 250 mg daily and that neither affected the renal clearance of iodide The thyroid glands of their patients had a lowered clearance of I^{131} resulting from the administration of both steroids Thus they conclude as did Berson and Yalow [1] that cortisone truly depresses thyroid function

The relation of the thyroid to the adrenal medulla is also unclear Thyrotoxic patients and animals show an increased sensitivity to epinephrin This has served as the basis for the Goetsch test in the diagnosis of hyperthyroidism [1 8] Soffer and his associates [1 9] have found that epinephrin will produce thyroid hyperplasia in dogs evidently through stimulation of thyrotrophin since its causes marked increase in circulating thyrotrophin in thyroidectomized animals

Botkin and Jensen [1] found that epinephrin administered to rats quickly produced a lowered iodine content in the thyroid gland with a decrease in serum iodine concentration whereas thyrotrophin caused an increased serum iodine with a lowered gland iodine Epinephrin possibly exerts its effects on the peripheral tissues thus increasing the demand for thyroid hormone If this is true immediate utilization by the tissues would cause a decrease in serum hormone which would in turn cause a release of pituitary thyrotrophin with restoration of normal blood thyroid hormone levels by increased output from the thyroid gland

INTERRELATIONS OF THE THYROID GONADS AND BREAST

Although there is a striking incidence of all types of thyroid disease in the female the relations between the thyroid and the ovary are not at all of the same order of significance as those between thyroid and pituitary

In normal animals and in animals receiving iodides the iodine concentration in the ovary is second to that found in the thyroid itself [160 161] The concentration of iodine in the ovary however is less than one fiftieth of the concentration in the thyroid The nature of this iodine has not been determined but it represents no significant amount of thyroxine iodine

During the sexual cycle of the female there is evidence of alteration in the physiological activity of the thyroid Chouke [16 163] and his fellow workers have found that the proliferative activity of the thyroid gland

as measured by mitotic changes, is greatest during the first week of the estrus cycle and decreases to a minimum about the tenth day Loeser[164] found increased thyrotrophic production and secretion following ovariectomy in guinea pigs On the other hand thyroidectomy in the rat is followed by a decrease in pituitary gonadotrophic activity[165] This decrease apparently involves chiefly the luteinizing rather than the follicle stimulating hormone according to Chu[166] His animals showed increased numbers of large follicles but no postcoital ovulation as in the normal

The menstrual pattern in hyperthyroidism and myxedema has been studied by Goldsmith and his associates[166a] who utilized endometrial biopsies and pregnanediol excretion as indices of phasic ovarian activity In thyrotoxicosis the predominant menstrual pattern was of oligomenorrhea with occasional amenorrhea The amenorrhea was usually caused by ovulatory failure with hypoestrinism When the menses were scanty or infrequent ovulation continued normally Amelioration of the thyrotoxic state usually resulted in restoration of a normal menstrual pattern even before complete euthyroidism occurred

In premenopausal myxedema, irregular and acyclic bleeding or amenorrhea usually occurred Ovulatory failure was the rule with occasional instances of normal physiologic menstruation Characteristically the myxedematous patient exhibited failure of ovulation with a continuous estrin effect on the endometrium and the development of metropathia hemorrhagica The defect in myxedema would therefore appear to lie in decreased production of the luteinizing hormone by the pituitary or in failure of ovulation despite adequate supplies of hormone The establishment of euthyroidism quickly brought about normal menstrual cycles

Excessive amounts of thyroid in the diet of growing rats has been found to prevent normal ovarian development[167] Conversely, estrogens may lower the iodine content of the thyroid,[168] while ovariectomy is followed by a relative increase in thyroid iodine[169]

In pregnancy marked changes occur in the thyroid There is increased demand for iodine with resultant goiter if the diet is deficient in iodine The blood iodine rises above normal at the third month and reaches a maximum at the seventh month[170] Corresponding with this hyperiodemia is an increased basal metabolic rate, the increased blood iodine probably represents elevated amounts of circulating hormone This hyperiodemia is not transmitted to the fetus[171] Whiteside[172] has reported abortion or fetal death in pregnant rabbits injected with thyrotrophin

and ascribes this effect to excessive thyroxine which has penetrated the placenta[172]

The physiologic rise in the protein bound iodine in human pregnancy[172a, 172b] is perhaps due to the increased estrogen production characteristic of pregnancy Engstrom and his co workers[172c] have demonstrated that the serum precipitable iodine rises with estrogen administration often increasing to the levels observed in mild thyrotoxicosis

Sexual activity itself appears to be affected by the thyroid only because of general metabolic changes Thus thyroidectomized male rats display no mating behavior yet the thyroidectomized female is capable of fertile breeding Young[173a] and Petersen[173b] and their associates have found that in the guinea pig there is no close relation between the thyroid and reproduction either in the male or female and that there is a wide range of thyroid activity compatible with reproduction Similarly a thyroidectomized bull produces fertile seminal fluid capable of successful artificial insemination[174]

The thyroid gland appears to be essential for mammary development particularly proliferation of the ducts Thus in thyroidectomized cows estrogen will not produce mammary growth unless thyroid is administered[175] Thyroidectomy produces inhibition of duct development in immature male rats but at the same time there is stimulation of alveolar development[176] Similarly thyroxine enhances the stimulating effects of progesterone and estrogens upon the growth of lobules and alveolar tissue in mice Thyroidectomy inhibits the ability of these mice to respond to progesterone and estrogen[177] Desiccated thyroid alone will cause duct proliferation and hyperplasia of the end buds in male mice Castrated male mice will not respond in this fashion to thyroid administration[178]

Interrelations of the Thyroid and the Pancreas

The relation of the thyroid to carbohydrate metabolism has been discussed in Part I Houssay and his associates[179] have extended their studies on this subject particularly with regard to alloxan and pancreatic diabetes in the rat The response in this animal has many remarkable differences from the reaction in the dog or the cat In the latter animal it will be recalled there was little influence on carbohydrate metabolism by thyroxine thyrotrophin or thyroidectomy In the dog on the other hand the administration of thyroid tended to aggravate existing diabetes and in general to have a diabetogenic effect In the rat thyroidectomy coun

teracted somewhat the diabetogenic action of alloxan Thiouracil treatment was even more antagonistic to the action of alloxan Thyroidectomy simultaneous with subtotal pancreatectomy, prevented the appearance of diabetes but as with the dog had no effect on manifest diabetes Thiouracil treatment acted in similar fashion Administration of thyroid to pancreatectomized rats caused premature appearance of diabetes but this type of diabetes disappeared gradually and permanently, despite continuous treatment with thyroid In animals not treated with thyroid permanent diabetes regularly followed pancreatectomy Finally the administration of thyroid to pancreatectomized diabetic rats resulted in complete disappearance of the diabetic state

The relation of these findings in animals to the thyroid and pancreas interplay in the human is certainly unclear Is man like cat, dog or rat The answer to this intriguing question must await more specific methods of study of the hormonal balance involved

Interrelations of the Thyroid and Thymus

Thyroid thymus interrelations are concerned chiefly with growth processes According to Gudernatsch [180] thyroid feeding produces acceleration of metamorphosis and cessation of growth of tadpoles whereas thymus feeding results in acceleration of growth and failure of metamorphosis Speidel [181] noted that the feeding of thyroid to tadpoles causes definite changes in the thymus the lymphocytes of the thymus and elsewhere were stimulated to mitotic proliferation Richter and Wislocki [182] however found hypoplastic thyroids and adrenals with enlarged thymus and lymph nodes in hypophysectomized rats

Sunder Plassmann [183] has described connections between the thyroid and thymus in the newborn consisting of large epithelioid cells with light nuclei which are controlled by the vegetative nervous system This author believes that thyroid secretion is fixed by the lymphocytic cortex of the thymus because he has noted atrophy of the thymus following thyroidectomy and hyperplastic changes in the thymus, when thyroidectomized patients are fed thyroid extracts

Rehn [184, 185] has investigated the function of the thymus in ten cases of exophthalmic goiter utilizing the method of Bomskov [186, 187] for detection of thymus hormone in urine Rehn found evidence of secondary hyperfunction of the thymus in some of these patients When iodine therapy relieved the thyrotoxicosis all evidence of thymus hyperfunction disappeared He believes that the myasthenia of exophthalmic goiter is the result of thymic hyperfunction

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PART III

ANTITHYROID GOITROGENS

Cyanates and Thiouracils

Compounds possessing antithyroidal properties fall into two general categories those that act without producing goiter such as iodine and radioactive iodine and those that cause marked hyperplasia of the thyroid and at the same time depress its function The latter group embraces the cyanides thiocyanates sulfonamides and thiourea with its derivatives This subject has been extensively reviewed by Williams[1] Riker and Wescoe Gargill and Lesses[3] and Greer[4]

The goitrogenic action of cabbage demonstrated in 19 9 by Chesney Clawson and Webster[4] was shown by Marine and his associates[5, 6] to be common to the entire genus of Brassica and to be due to contained cyanides The condition produced was in essence an iodine deficiency goiter, since it could be prevented by administered iodine and was due to increased thyroid activity caused by depressed oxygen consumption from the cyanide Depressed oxygen utilization increases thyroid activity goiter results if iodine is lacking in the face of added demands on the thyroid gland

That thiocyanates exert a goitrogenic and antithyroidal effect was first accidentally observed by Barker[7] in hypertensive patients under treatment with potassium thiocyanate Many similar cases subsequently reported have been reviewed by Estes and Keith[4] These goiters occur in about 4 per cent of such patients[8] and are characterized by thyroid hyperplasia the signs and symptoms of myxedema and occasionally by exophthalmos and by an increased *urinary excretion of inactivated* thyrotrophic hormone Rawson and his co workers[10, 11] believe that the thiocyanate prevents the synthesis of thyroid hormone at some point distal to the uptake of iodine since they were able to demonstrate excessive uptake of radio iodine by thiocyanate induced goiters *Decreased hormone* elaboration leads to hypometabolism with stimulation of the anterior pituitary and increased production of thyrotrophic hormone Thyroid hyperplasia results without a corresponding increase in hormone output — a hyperplasia of frustration The administration of desiccated thyroid prevents or relieves thiocyanate goiter

The more active substances were derivatives of thiouracil the less active possessed an aminobenzene group such as the sulfonamides and were a fourth as active as thiouracil The most potent of the former group proved to be 6 N propyl thiouracil in animal assays

To this periodic table of antithyroidal goitrogens established by Astwood other investigators [4-7] have added and undoubtedly will continue to add various active compounds since the slightest shift in chemical structure or linkage produces marked pharmacological differences

Since the morphological and physiological effects of these compounds particularly of thiouracil have been abundantly studied an accurate postulation of the mechanism of hormone inhibition can be constructed Thiouracil retards growth induces cretinism in newborn rats and antagonizes the effects of injection of the growth hormone of the anterior pituitary body [31 3] The presence of the pituitary is essential for the production of goiter with these drugs [13 0 1] since no thyroid hyperplasia occurs in hypophysectomized animals following their administration in fact the thyroid gland regresses as in untreated hypophysectomized animals The goitrogenic effect results from pituitary stimulation and not from direct action by these compounds on the thyroid parenchyma (Plate 5)

No increase of thyrotrophic hormone is demonstrable in the blood or hypophysis of rats treated with thiourea or sulfadiazine in fact there is a decrease as compared with marked increases found in thyroidectomized animals [33] Animals pre treated with thiourea and then thyroidectomized showed an increase of thyrotrophic hormone in the blood and a decrease in the pituitary gland Gordon and his associates [33] state Thiourea and sulfadiazine by depressing the formation of active thyroid principle cause an increased release of thyrotrophin from the pituitary into the blood where however it appears in reduced amount because of its removal and increased utilization by the enlarging thyroid gland Although the decreased amount of the thyroid stimulating hormone found in the pituitary glands of the drug treated animals is not explained it has been shown by Albert and his associates [34 3 36] that physiologically inactive amounts of these goitrogens augment the action of the thyroid stimulating hormone when mixed with it in vitro and when administered in vivo This synergism is also illustrated by the greater hyperplasia of the thyroid gland in animals treated with both thiouracil and thyrotrophin as compared with that in animals treated with either alone

It has been noted above (Part II) that elementary iodine will inactivate thyrotrophin quite completely when the two are mixed in the test tube

Thiocyanate therapy may also cause acute goiter, clinically resembling thyroiditis [1] and pathologically showing extreme parenchymatous hypertrophy and hyperplasia [11] but without papillary infolding or lymphocytic infiltration While the colloid stains well the irregularity of the acini and a tendency toward invasiveness simulate neoplasia

The antithyroidal and goitrogenic properties of the cyanides and cyanates were of experimental and toxicologic interest but failed of clinical application In 1941 however, British and American investigators simultaneously revived interest in the chemotherapeusis of Graves' disease by parallel studies of new antithyroidal goitrogens Kennedy and his co workers [14] found that Brassica seed diets produced large goiters in rats in spite of simultaneously administered iodide, the goiters required the presence of thyrotrophic hormone for development or maintenance since they did not develop in hypophysectomized animals and regressed after hypophysectomy [1] [16] The active goitrogenic principle was demonstrated to be thiourea or allyl thiourea [17]

Meanwhile Richter and Clisby [18] in searching for an improved rat poison discovered that phenyl thiourea caused marked hyperplasia of the thyroid gland Somewhat earlier the MacKenzies and McCollum [19] found that sulfaguanidine caused marked thyroid hyperplasia

In this initial phase of study chief emphasis had been placed on goitrogenesis — an iteration of the early work with the cyanides and cyanates Astwood and others [0] and simultaneously the MacKenzies [1] directed attention to the more important effect of these compounds as inhibitors of thyroid function Both groups of investigators first studied the sulfonamides and thiourea finding the latter many times more active as an antithyroidal drug Both compounds caused thyroid hypofunction, with reduced oxygen consumption and impairment in growth and development The thyroid glands were enlarged, hyperemic and hyperplastic with decreased colloid and increased acinar-cell height, papillary infoldings of the epithelium were frequently observed Omission of the drugs was followed by histological and physiological return to normal (Plates 3 and 4)

The shifting of emphasis from goitrogenesis to antithyroidal activity was followed by widespread research into the compounds that maximally depressed thyroid function and were only incidentally productive of thyroid enlargement Thiourea thiouracil and their derivatives were found to be the most potent compounds for inhibiting thyroid function In a study of over -20 substances Astwood Bissell, and Hughes [3] found two types of chemical structure associated with antithyroidal activity

Plate 3

4 Gross appearance of 3 thyroid glands dorsal aspect From left to right these are an untreated animal a 6-day old animal treated from the 21st day with 2 per cent sulfaguanidine in the diet and a 65 day-old rat treated from the 1st day with 5 per cent sulfaguanidine in the diet

5 Thyroid glands of female rats All sections were made in the same plane at right angles to the trachea and uniformly at a level near or through the parathyroids Hematoxylin and eosin

6 37 day-old animal which had received 5 per cent sulfaguanidine in the diet for 15 days

7 41 day-old rat hypophysectomized at 6 days of age and given 2 per cent sulfaguanidine in the food for 15 days This gland is indistinguishable from that of an untreated hypophysectomized rat

8 9 10 11 Glands taken at 2 4 and 12 days respectively after the beginning of treatment with 1 per cent thiourea in the drinking water at 21 days of age Treatment was discontinued at 7 days and figure 10 shows the degree of regression occurring in 5 days The epithelium is flat and colloid has reaccumulated but there is little decrease in size

From Astwood E B Sullivan J Bissell A and Tyslowitz R Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat Endocrinology 1943 xxxii 2 0 25

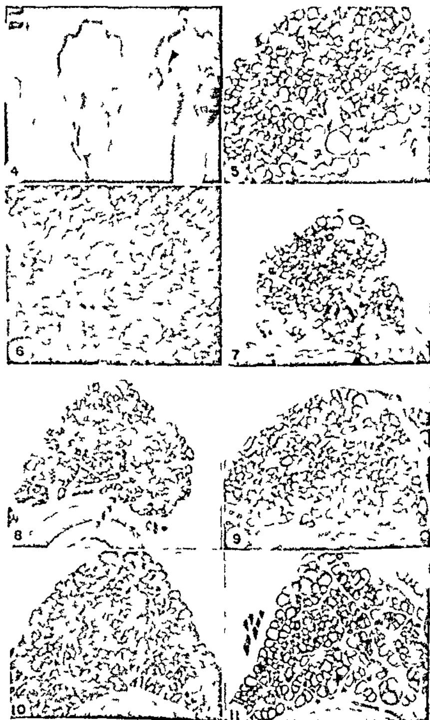

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Plate 4

12 Thyroid from a 33 day-old rat which had received a diet containing 2 per cent sulfaguanidine and 2 per cent thyroid powder for 13 days The gland is atrophic and resembles the gland in figure 7

13 Effect of 10 days treatment with 0 1 per cent thiourea and 1.0 per cent potassium iodide in the drinking water A minimal degree of inhibition of the thiourea is seen which is considered to be an effect of toxic amounts of potassium iodide

14 15 16 Glands from animals given 2 per cent sulfaguanidine in the food from the 21st to 51st days of life 14 *Degree of hyperplasia induced by this treatment* 15 *Gland taken 5 days after hypophysectomy the drug being continued post-operatively* 16 *Thyroid of an unoperated animal 5 days after the drug was discontinued* 15 and 16 show a reaccumulation of colloid and a flattening of the follicular epithelium

17 18 Glands of treated animals showing unusual types of hyperplasia 17 *An adult treated with 1 per cent thiourea for 68 days* 18 *60 day-old animal which had* received 0 5 per cent sulfapyridine in the drinking water for 11 days The follicular cells appear to be breaking away from their normal attachments and floating free in the colloid free follicular spaces

From Astwood L B Sullivan J Bissell A and Tyslowitz R Action of certain *sulfonamides and of thiourea upon the function of the thyroid gland of the rat Endo*crinology 1943 xxxii 210-25


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From Astwood E B Sullivan J Bissell A and Tyslowitz R Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat Endocrinology 1943 xxxii 210-5



Plate 5

(upper) Thiouracil treated male and normal male litter mate control (age 10 weeks)
(lower) Same individuals as in upper (age 26 weeks) From Hughes A M Cretinism in rats induced by thiouracil Endocrinology 1944 xxxiv 69-76

Removal of most of the iodine results in reactivation of the hormonal material Albert and his co workers[34] have extended this original observation in a study of the in vitro effects of goitrogens and other reducing agents The goitrogens utilized were all thiourea derivatives including those that have been applied clinically An iodinated extract of thyrotrophin physiologically inactive was restored to potency by treatment in vitro with various thiourea derived goitrogens As these are reducing compounds various non goitrogenic reducing agents were studied and found to have similar but less marked effects in the reactivation of iodinated thyrotrophin

In addition to their ability to reactivate iodinated thyrotrophin these goitrogens were found capable of greatly augmenting thyrotrophic activity as measured by bio-assay[3] This augmenting effect was still present after removal of the goitrogen prior to bio assay so presumably there had been an alteration in the thyrotrophin itself which led to its increased activity

The capacity of thiourea derived goitrogens to augment thyrotrophin as well as to reactivate iodinated thyrotrophin was found to hold true in the living organism as well as in the test tube[46] In these experiments day old chicks were injected with iodinated thyrotrophin or active thyrotrophin after having previously received various amounts of thiouracil Marked augmentation of thyrotrophic potency up to 100 per cent and reactivation of iodinated thyrotrophin up to 50 per cent occurred in the thiouracil fed chicks

Whereas the goitrogenic action of the cyanides and probably of the cyanates could be inhibited by iodides this was not found to be true with the thiourea derivatives[37] which were in fact iodine resistant goitrogens But thyroxine or desiccated thyroid did prevent and abolish the goitrogenic and antithyroidal effect of these compounds as well as of the sulfonamides[1] indicating that they do not function by inhibiting the action of the thyroid hormone in the blood or peripheral tissues Moreover Mulkiel[38] has found no destructive or inactivating effect of thiouracil and sulfaguanidine on endogenous circulating thyroxine

The effect of the antithyroidal goitrogens on the metabolism of iodine has been explored by conventional technics and through the use of radio active iodine Thiouracil and sulfadiazine cause nearly complete disappearance of iodine from the thyroid gland in five days[34] This effect is inhibited by removal of the hypophysis or administration of thyroxine Iodine reaccumulates after withdrawal of the drug but this reaccumulation is retarded by hypophysectomy or the administration of thyroxine



Plate 5

(upper) Thiouracil treated male and normal male litter mate control (age 10 weeks)
(lower) Same individuals as in upper (age 6 weeks) From Hughes A M Cretinism in rats induced by thiouracil Endocrinology 1944 xxxiv 69 76

collected radio-iodine in larger quantities than did those of the controls, in amounts similar to those collected by glands made hyperplastic with injections of thyroid stimulating hormone. The inhibition of iodine collection resulting from thiouracil in the intact thyroid gland contrasts sharply with the in vitro studies previously described[4, 13] but both sets of experiments confirm the hypothesis that thiouracil interferes with hormone synthesis by interfering with the metabolism of iodine. Thiouracil inhibited collection of radio-iodine by normal chick thyroid and by that made hyperplastic through thyroid stimulating hormone or thiouracil. Salter, Cortell and McKay[47] reached similar conclusions concerning the role of thiouracil—it prevents the conversion of iodide to diiodotyrosine and thyroxine without, however, impeding the synthesis of uniodinated thyroid protein.

Chaikoff and his associates[48] have confirmed the depressing effect of potassium thiocyanate on the uptake of radio-iodine by thyroid tissue either in vitro or in living animals maintained on an iodine poor diet. Following the disappearance of potassium thiocyanate from the circulation, the whole gland does have an increased uptake of radio iodine but this increase is not apparent when expressed in terms of unit weight of tissue. Thus the drug interferes with the removal of iodine from the circulation when iodine is not readily available in the diet. It also inhibits conversion of inorganic iodide to diiodotyrosine and thyroxine as shown by low thyroxine content of the gland and decreased levels of protein bound iodine in the blood. Vanderlaan and Bissell[49] have confirmed this course of events by showing that rats fed propylthiouracil readily take up radio iodine in their thyroid glands but retain it only for a short time possibly because it is not hormone bound and that in the presence of both propylthiouracil and potassium thiocyanate there is delayed and only moderate iodine uptake by the gland. They conclude that in the presence of thiocyanate the ability of the thyroid gland depleted of iodine to take up injected iodine is considerably impaired.

Vanderlaan and Vanderlaan, while studying the iodine concentrating mechanism of the rat's thyroid, found that thiocyanate interfered significantly with this mechanism by preventing the uptake of iodide as such and also by causing discharge of iodide stored in the thyroid. Astwood had previously shown that the thyroid could concentrate iodine independently of its ability to manufacture hormone. The iodine initially absorbed by the gland was shown by the Vanderlaans to be present as iodide that was ultra filtrable and behaved as iodide potentiometrically. These investigators have introduced the concept of a gradient between

The relation between the dose of thiouracil and thyroid weight and iodine content is quantitative enough to be used for the assay of new compounds[39, 40]

By in vitro studies of thyroid slices with radioactive iodine Franklin and Chaikoff[41] found that the sulfonamides inhibited the formation of diiodotyrosine and thyroxine but did not alter the absorption of inorganic iodide from the surrounding medium Thiouracil and thiocyanate were similarly shown by these investigators[4] to depress or inhibit the formation of thyroxine and diiodotyrosine in vitro They differed in their effect on iodine concentration by thyroid slices, thiouracil having little effect and thiocyanate causing marked depression of iodine uptake by the surviving tissues

The inability of large amounts of iodine to overcome the stasis of hormone production caused by thiourea was demonstrated in rabbits by Baumann Metzger and Marine[37] who showed that the drug caused rapid decrease in both thyroxine and non thyroxine iodine in the gland itself with excretion of the excess iodine in the urine Further studies in vivo with radio iodine have confirmed the result of the studies in vitro—namely that thiouracil interferes in the living animal with the incorporation of iodine into thyroxine and diiodotyrosine in the thyroid gland[43] and thus causes cessation of hormone synthesis

Further details of the mechanism of action of thiouracil on iodine metabolism have been supplied by studies on the chick with radio iodine It was first demonstrated that thyrotrophic hormone produces thyroid hypertrophy within 24 hours[44] but no increased iodine uptake occurred until hyperplasia was marked This accelerated uptake was not maintained with continued stimulation In addition thyrotrophic hormone caused early and striking acceleration in the loss of radio iodine from the gland so that 75 per cent of the quantity initially stored was lost during the first day This was interpreted as being due to accelerated secretion of thyroid hormone from the gland induced by thyrotrophic stimulation

Next a comparison was made of the effects of thiouracil and of thyrotrophic hormone on the collection of radio iodine and on the histology of the thyroid gland in the chick[4, 46] The histological changes produced were indistinguishable except for a lag of five days in the appearance of alterations caused by thiouracil Within an hour after the injection of thiouracil however maximal inhibition of the uptake of radio iodine occurred with a gradual loss of this inhibitory effect over 24 hours Following the withdrawal of thiouracil the glands of the treated chicks

collected radio iodine in larger quantities than did those of the controls in amounts similar to those collected by glands made hyperplastic with injections of thyroid stimulating hormone The inhibition of iodine collection resulting from thiouracil in the intact thyroid gland contrasts sharply with the in vitro studies previously described [4, 43] but both sets of experiments confirm the hypothesis that thiouracil interferes with hormone synthesis by interfering with the metabolism of iodine Thiouracil inhibited collection of radio iodine by normal chick thyroid and by that made hyperplastic through thyroid stimulating hormone or thiouracil. Salter Cortell and McKay [47] reached similar conclusions concerning the role of thiouracil—it prevents the conversion of iodide to diiodotyrosine and thyroxine without however impeding the synthesis of uniodinated thyroid protein

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the concentration of iodide in the serum and in thyroid tissue Over a considerable range of serum iodide concentration they found this gradient to be constant Thus the concentration of iodide in the thyroid could be viewed as a function of the level of the serum iodide In normal glands the concentration of iodide was 25 times that of the serum whereas in animals pretreated with propylthiouracil there existed a ten fold increase in this concentrating power

A new technique for the assay of antithyroid compounds in normal human subjects has been described by Stanley and Astwood The uptake of tracer doses of radio iodine was first determined in clinically normal persons and then the inhibitory action of a single dose of various thiourea and thiouracil compounds upon this uptake was measured by a Geiger Muller counting tube which was placed directly over the thyroid gland Serial counts were taken at frequent intervals With this method 32 compounds were assayed in 90 subjects and it was found that the values realized differed considerably from those found by rat or chick assay and indeed agreed much more closely with clinical appraisals of relative potency It is of interest that sulfadiazine, the only member of the aminobenzene group of antithyroid compounds tested, was found to be inert by this method contrasting very sharply with its considerable effectiveness in animals

The evidence that biosynthesis of thyroxine is intracellular aerobic and enzymatic has been discussed in Part 1 The iodination of tyrosine to diiodotyrosine requires liberation of iodine from iodide The formation of diiodotyrosine and thyroxine is linked with aerobic oxidations involving the cytochrome-cytochrome oxidase system [3] The effect of the sulfonamides and thiouracil on this enzyme system is controversial Franklin and Chaikoff [41] observing no effect with the sulfonamides and Dempsey [4] noting that thiouracil readily inhibited the peroxidase reaction in thyroid tissue but did not affect the cytochrome oxidase reaction McShan Meyer and Johansson found no inhibition of cytochrome oxidase or of succinoxidase in thyroid tissue by sulfonamides and thiouracil On the other hand Paschkis and his co-workers [6] report that thiouracil and the sulfonamides inhibit the cytochrome-oxidase in vitro as well as in the thyroid gland itself Bevelander [7] after studies on sea urchin egg development concluded that thiourea acts by inhibition of enzyme systems necessary for the growth of the sea urchin Tipton and Nixon [78] observed significant depression of succinoxidase and cytochrome oxidase in the liver of rats

Thiouracil acts by preventing iodination and hormone synthesis but it is still not clear whether it acts as an anti oxidant through depression

of the enzyme systems or by some mechanism other than inhibition of oxidation

The differentiation of the antithyroidal and goitrogenic actions of thiourea derivatives sulfonamides and para aminobenzoic acid (PABA) by the response of the organism to iodine administration has been established by MacKenzie [9] Small amounts of iodide markedly inhibited the thyroid enlargement as measured by weight caused by thiouracil but had no significant effect on the thyroid hyperplasia Large amounts of iodide had no further effect on thyroid weight but did suppress the hyperplasia With very large amounts of iodide the morphological response to thiouracil was repressed and in fact resembled the glands found in thyrotoxicosis following the administration of iodides i e reduced hyperemia decreased cell height colloid filled follicles but no complete suppression of epithelial hypertrophy

The administration of iodide to sulfaguanidine treated rats did not reduce thyroid weight or inhibit the degree of hyperplasia There was instead a potentiation of the goitrogenesis effected by the sulfaguanidine with increased weight and some tendency toward decreased colloid content MacKenzie notes This is probably the only condition thus far described in which iodide does not have an inhibiting effect on thyroid hyperplasia

Iodide administration in rats fed PABA had an effect similar to that found in the rats to whom the thioureas were administered — namely inhibition of goitrogenesis and hyperplasia The mechanisms may be different but the end results are the same so far as the thyroid gland is concerned

Further insight into the action of the goitrogens may eventually be gained through recent knowledge of their antibacterial and antitoxic effects Thus Weinstein [r] and Strandskov and Wyss [81] have found that thiourea is bacteriostatic for gram negative organisms inhibiting their growth and metabolism Zahl and his co workers [1] have demonstrated that both thiouracil and PABA have a protective effect against salmonella endotoxin apparently through interference with thyroid activity

Thiourea not only depresses enzymatic and bacterial metabolism but also disturbs the biochemical balance of the organism sufficiently to produce tumor formation Thus Purves and Griesbach [11] found that the prolonged administration of thiourea to rats resulted in the formation of thyroid adenomas many of which ultimately developed the histological characteristics of adenocarcinoma with blood vessel invasion and pulmonary metastases (Plates 6 7 8 9)

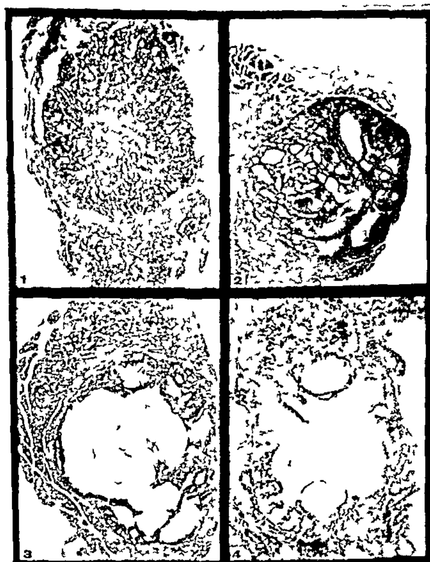

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Plate 6

1 Thyroid of rat after 17 month of rape seed diet One large several smaller adenomata Little normal thyroid tissue remaining Azan Stain

2 17 months rape seed diet Adenoma forming nodule projecting from the thyroid surface Compressed thyroid tissue forming a pseudocapsule H & E Stain

3 17 months rape seed diet Large adenoma showing cystic spaces filled with dilute colloid The darker staining of the adenoma tissue is apparent Azan Stain

4 Part of same tumor as 3 showing mechanism of formation of cystic spaces by rupture of acinar walls H & E Stain

From Griesbach W E Kennedy T H and Purves H D Studies on experimental goiter VI Thyroid adenomata in rats on Brassica seed diet Brit Jour Exper Path., 1945 xxvi 18 24

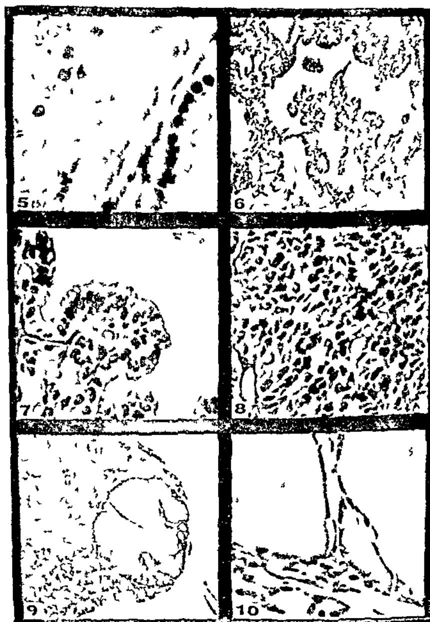

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Plate 7

5 Top left normal hyperplastic thyroid tissue Lower right edge of adenoma, showing the columnar form and darker staining nuclei of the adenoma cells H & E Stain

6 Adenoma of 1 showing papillary type of epithelial growth Azan Stain

7 Part of 6 Azan Stain

8 From an adenoma showing undifferentiated type of growth H & E Stain

9 17 months rape seed diet thyroxine injected during last three weeks The cystic adenoma is filled with dense colloid and the epithelium is flattened H & E Stain

10 Part of 9 showing flattened epithelium after thyroxine treatment H & E Stain

From Griesbach W E Kennedy T H and Purves H D Studies on experimental goiter VI Thyroid adenomata in rats on Brassica seed diet Brit Jour Exper Path., 1945 xxvi 18 4

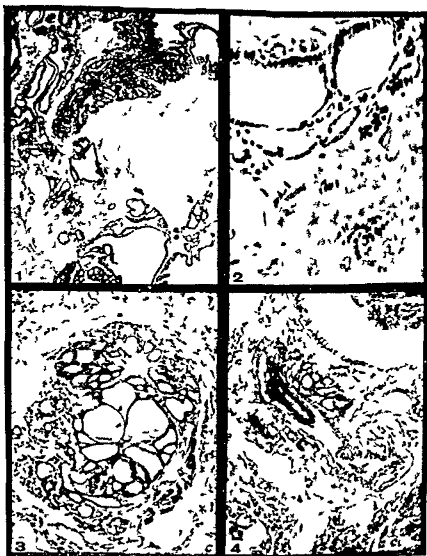

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Plate 8

1 Thyroid gland of Rat No 1 showing adenocarcinoma Colloid accumulation and areas of papillary growth are shown The wall of the vein to the right of the figure is extensively invaded by the tumor H & E Stain

2 Another field of the section shown in 1 showing tumor cells in contact with the blood stream H & E Stain

3 Metastasis in lung of Rat No 1 The central area containing large acini is surrounded by an area characterized by imperfect acini formation H & E Stain

4 Lung of Rat No A metastasis is situated inside a branch of the pulmonary artery An extension of this growth is infiltrating the tissues outside the artery H & E Stain

From Purves H D and Griesbach W E Studies on experimental goiter VII Thyroid carcinomata in rats treated with thiourea Brit Jour Exper Path 1946 xxvii 294 7

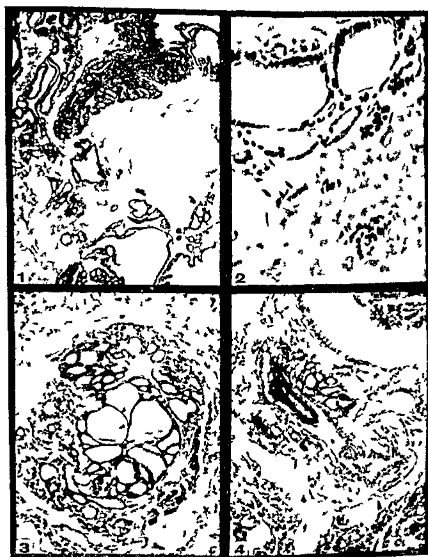

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Plate 9

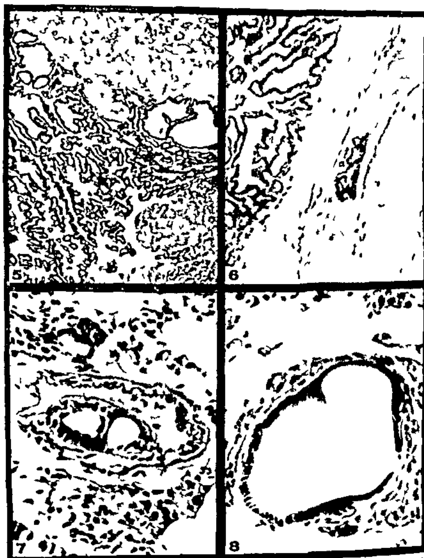
5 Thyroid gland of Rat No 2 showing at the top of the figure some normal thyroid tissue Below this is adenocarcinoma and at lower right the edge of a nodule of fetal adenoma H & E Stain

6 Thyroid gland of Rat No 2 showing thyroid carcinoma on the left In the center is a vein containing carcinoma tissue in the lumen H & E Stain

7 Lung of Rat No 2 showing a branch of the pulmonary artery in cross section The artery contains a small thyroid metastasis consisting of two acini containing colloid The metastasis is covered with endothelium and the remainder of the lumen is patent and contains blood H & E Stain

8 Lung of Rat No 2 showing a thyroid metastasis consisting of a single acinus distended with colloid H & E Stain

From Purves H D and Griesbach W E Studies on experimental goiter VII Thyroid carcinomata in rats treated with thiourea Brit Jour Exper Path 1946 xxvii 294 7


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tration in the body or in the thyroid gland in relation to antithyroidal activity but no parallelism could be established Storage of these goitrogens in the thyroid gland was clearly not the factor that determined their thyroid inhibiting effect

Other Antithyroidal Agents

The effectiveness of the antithyroidal goitrogens depends on their interference with the production of thyroid hormone They do not in themselves antagonize or neutralize the effect of circulating thyroxine so that they are antithyroidal by indirection rather than specifically Recently certain compounds have been claimed to be particularly antagonistic to thyroxine itself Carter and his collaborators [*] found a substance in ox and whale liver and in human urine—identified as paraxanthine (1 7-dimethylxanthine)—that was capable of converting the temperature heart rate curve of the summer frog s heart into the curve of the winter frog s heart This substance which was isolated in crystalline form appeared to counteract the effects of thyroxine in rats Barker and Williams [78] however were unable to find significant antithyroidal action from this drug as measured by effects either on oxygen consumption or on tadpole metamorphosis It had no observable result when given to a thyrotoxic patient for a period of 11 days

Mansfeld extracted from the thyroid gland and human serums crystalline substances called thermo thyrin A and B that are capable of producing as much as a 30 per cent lowering of oxygen consumption in rats This work has not yet been confirmed but the compounds involved may be related to certain structural analogues antagonistic to thyroxine investigated by Wooley [80] These newly synthesized ethers of N-acetyl diiodotyrosine counteracted the pharmacological effects of thyroxine on tadpoles The presence of an iodine atom or atoms in a benzenoid nucleus of a compound itself devoid of thyromimetic action is a necessary characteristic for this inhibitory effect Niemann [81] has commented that the relationship of the structure of the inhibitor to that of thyroxine may indeed be of a remote nature

Lawson and Rimington [*] *in searching for a natural antithyroidal thiol* compound studied ergothioneine a normal constituent of the blood Ergothioneine is methyl betain of 2-thiol-histidine When administered to rats it was found to exert an antithyroidal effect comparable to that of thiouracil Clinical studies have not yet been reported

The anatomical effects produced in the human thyroid gland by thiouracil have been studied chiefly in the hyperplastic gland of Graves' disease The size of the gland may increase, decrease, or remain unaltered, but the gross increases in human beings have not been so striking or so constant as those in experimental animals Prolonged treatment has usually resulted in a decrease of the gland[64] unless myxedema supervenes Histologically, however, there is great similarity to the experimental effect with increased thyroid hyperplasia, loss of colloid and increased vascularity[6, 68] Changes in the pituitary gland similar to those found in animals—increased basophilism and absent eosinophilism—have been reported[6]

Physiologically, thiouracil decreases the basal metabolic rate, frequently at the same rate as iodine[6, 68] and in many cases causes clinical myxedema if continued for several months[68, 69] Myxedema however has not yet been readily produced by thiouracil in persons with normal thyroid function,[68] the normal economy evidently possessing adequate homeostatic mechanisms for resisting the usual goitrogenic and thyroid depressing effects of this compound Following the administration of thiouracil in Graves disease the uptake of tracer doses of radio iodine is greatly diminished with an increased urinary excretion[6] as previously described in animal studies The hormonal iodine of the blood returns to normal[70] the blood cholesterol rises[71] the calcium phosphorus and protein balances become more positive and creatinuria decreases[7] In general the physiological effects produced are such as would occur with amelioration of thyrotoxicosis and a return to the euthyroid state These changes which occur far more regularly than with iodine therapy may take from several weeks to several months for completion

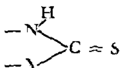
The absorption, distribution and metabolism of thioureas and thiouracils have been studied by Williams and his co workers[3, 74] through application of methods of considerable accuracy to all the tissues and fluids of the body Thiouracil is rapidly absorbed from the gastro intestinal tract and appears in the blood stream within 15 minutes after ingestion It is present chiefly in the cells of the blood, bound to protein and rarely in concentrations above 6 mg per cent It diffuses into all the tissues and fluids where about half of it is degrated A small amount is destroyed in the gastro intestinal tract and about one third is excreted unchanged in the urine It passes through the placenta in biologically active quantities It is excreted in milk and can produce cretinism in suckling animals[7]

Various thiouracils have been studied further[4] with regard to concen

A new antithyroidal goitrogen differing chemically from previously known substances has been discovered by Bull and Fraser.[83] They observed three patients who had developed myxedema and goiter following the prolonged application of resorcinol ointment to varicose ulcers of the legs. Biopsies of the thyroid gland in these patients showed intense hyperplasia similar to that found after the thiouracils. The level of the protein-bound iodine in the blood was extremely low but the uptake of radioactive iodine was high as soon as the resorcinol applications were omitted. In this manner the action of resorcinol was like that of the thiocyanates and the thiouracils, depressing iodine binding by the thyroid gland with resultant hyperplasia and permitting great iodine avidity upon omission of the goitrogen. Further studies by Doniach and Fraser[84] of the effects of resorcinol upon the thyroid gland of the rat indicated that, like the thiouracil compounds, this drug markedly depressed iodine uptake and organic binding of iodine.

A goitrogen with marked stimulatory adrenal as well as antithyroidal effects is Amphenone B, a substituted desoxybenzoin. Hogness and his associates[85] have shown that this compound inhibits the incorporation of I^{131} into thyroid protein both in vivo and in vitro with a potency equal to that of propylthiouracil and without any effect on the rate of release of radio-iodine from the rat thyroid. Prolonged administration to rats produced adrenomegaly which was associated with increases in adrenal ascorbic acid and cholesterol concentrations. Determinations of liver glycogen, circulating eosinophiles and thymus weight indicated that the enlarged adrenals were capable of responding to ACTH or cold stimulus by secreting an increased quantity of steroids. The response in Amphenone-B'-treated animals was greater than that of the controls.

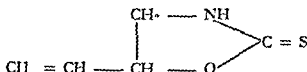
Greer,[86] in a review of the relation of plant and animal products to goitrogenesis, points out that the thionamide grouping is characteristic of the antithyroidal goitrogens active in man, and that vinyl thiooxazolidone is the only antithyroid compound that has been isolated from ruta





Thionamide Grouping

baga and other members of the cabbage family. This compound exists in nature in combined form, possibly as a glycoside. If the roots or seeds



L-5-vinyl-2-thiooxazolidone

are boiled, baked, or steamed, no thiooxazolidone can be isolated, but if the raw food is finely ground and suspended in water, the thiooxazolidone is formed in a few minutes. The heated inactivated material will, however, yield thiooxazolidone if it is subsequently treated with a purified enzyme preparation from the unheated plant. The compound has never been isolated from cabbage leaves and this probably accounts for the fact that cabbage as ingested by man seems to have very little antithyroid activity. Greer concludes that while a sporadic goiter in man may occasionally be due to the ingestion of goitrogenic foods, very few instances of thyroid enlargement not due to iodine lack have yet been explained. It is possible, of course, that other naturally occurring goitrogens may be isolated in the future from other foods and that these may not require enzymatic liberation to acquire antithyroidal activity.

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PART IV

THE METABOLISM OF IODINE AND ITS RELATION TO THE STRUCTURE AND FUNCTION OF THE THYROID

Absorption and Excretion of Iodine

The absorption and excretion of iodine involves the following factors: (1) the level of iodine intake, (2) the type of iodine compound administered, (3) the state of thyroid function, and (4) the route of administration. Elmer[1] and Salter[2] have reviewed this subject from the standpoint of iodine balance. Techniques utilizing radioactive isotopes have added further information on the absorption, storage, and excretion of iodine.

In normal persons maintained on a low intake of iodine, Puppel and Curtis[3] found that about 70 per cent of the iodine was excreted in the urine, 15 per cent in the feces, and the remaining 15 per cent in the perspiration. Negative iodine balance readily ensued with a sufficiently low intake of iodine.

With quantities of iodine ranging from 20 to 440 mg. daily, amounts markedly in excess of any physiological requirements, Nelson and his associates[4] found that iodine was rapidly absorbed, with plasma iodine concentrations running parallel to the level of intake. The absorption was both rapid and complete, since no significant quantity of iodine was recovered from the feces. Iodine disappeared from the plasma at a relatively uniform rate in accordance with the level of concentration, so that after 24 hours the plasma iodine concentration had returned almost to normal. About 75 per cent of the iodine was excreted in the urine within the first 3 days after a large intake. Between 2 and 10 per cent of the iodine was excreted in the perspiration, as had been previously demonstrated by von Fellenberg.[5] In profuse sweating the latter had observed excretion values of over 30 per cent. The fecal excretion was found negligible by Nelson,[4] but Cole and Curtis[6] reported that 6 to 7 per cent of the iodine intake was excreted in the feces.

In non-toxic nodular goiter, Puppel and Curtis[7] noted excretion values

balance in these individuals but excessive amounts of ingested iodine did effect a positive iodine balance (Figs 16 17 18 19 20)

Iodine in organic combination such as in di iodotyrosine and thyroxine is readily absorbed from the gut with minimal fecal loss Thyroxine itself is easily absorbable if administered in alkaline solution but is largely excreted in the feces when administered in its dry crystalline and quite insoluble state Thyroid substance is readily assimilated and in myx

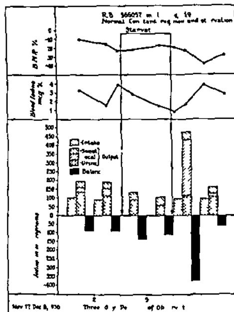


Fig 17 The effect of starvation on the normal iodine balance Note the continued negative balance

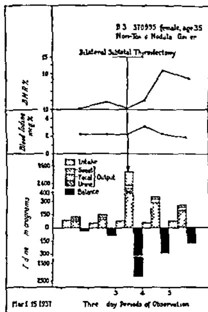


Fig 18 Non toxic nodular goiter presents a normal negative iodine balance on a low iodine intake Note the effect of thyroidectomy

From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574-87

edema produces a greater effect than its contained thyroxine (see Part 1)

The significance of the form in which iodine is administered has recently been emphasized by Dvoskin [8] who has successfully demonstrated the thyroxine like action of elemental iodine in the experimental animal Many previous investigators had demonstrated that elemental iodine administered parenterally would induce metamorphoses in the axolotl even after thyroidectomy or hypophysectomy This effect could not

of iodine entirely comparable to those in normal human beings at corresponding levels of intake, whereas in thyrotoxicosis the same author[3]

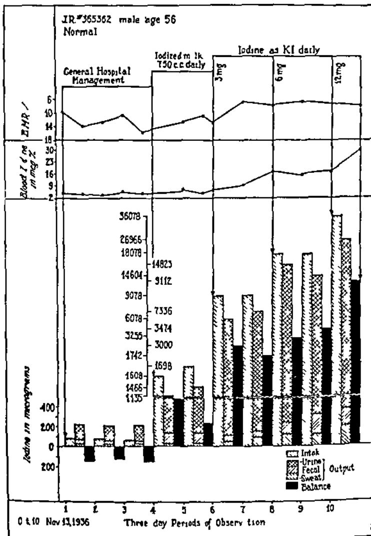


Fig 16 The iodine balance in a normal individual Note the negative iodine balance on a low iodine intake and the effect of increasing the intake From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574 87

demonstrated a great increase in iodine excretion especially in the feces A normal iodine intake in thyrotoxic patients resulted in negative iodine

to prevent thyroid hypertrophy and increase in gland weight by the administration of the goitrogens thiouracil and sulfadiazine

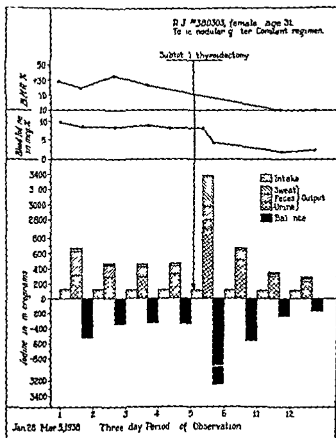


Fig 20 The increased negative iodine balance of toxic nodular goiter Note the increased urinary excretion over normal Note the effect of thyroidectomy From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cvııı 5 4 87

By these criteria elemental iodine when administered subcutaneously was found to have a thyroxine like action that was not evident on oral administration

Iodine Stores in the Body

While iodine storage in the organism occurs mainly in the thyroid gland significant concentrations of this element occur throughout the

be produced by addition of elemental iodine to the water in which the axolotl was kept The subcutaneous injection of elemental iodine in the rat or chick produced effects similar to those produced by thyroxine whereas sodium iodide when injected had little thyroxine like activity The methods utilized in these studies as a measure of thyroxine like activ

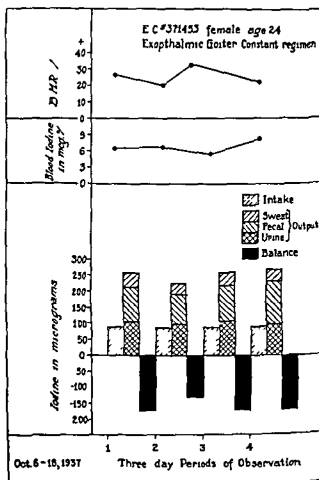


Fig 19 The increased negative iodine balance of exophthalmic goiter Note the increased fecal excretion over normal From Curtis G M and Puppel I D The iodine metabolism in exophthalmic goiter Ann Surg 1938 cviii 574 87

ity were (1) the ability to restore and maintain growth after thyroidectomy, (2) the ability to restore the adrenal gland weight of thyroidectomized rat to normal (3) the ability to cause involution of thyroid epithelium and to decrease gland weight in normal rats, and (4) the ability

to prevent thyroid hypertrophy and increase in gland weight by the administration of the goitrogens thiouracil and sulfadiazine

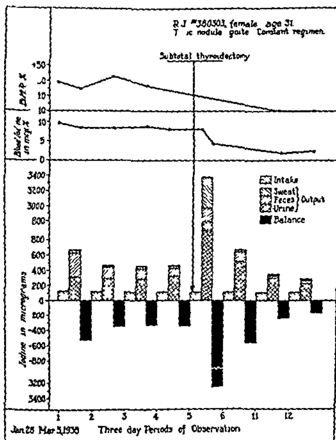


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Iodine Stores in the Body

While iodine storage in the organism occurs mainly in the thyroid gland significant concentrations of this element occur throughout the

body chiefly in the form of iodides Salter[9] has elaborated available knowledge of intrathyroidal and extrathyroidal iodine storage into a concept of iodide circulation This circulation permits release of hormonal iodide for its metabolic function and also allows the utilization of released iodide for re-synthesis of thyroid hormone Iodine in the tissues is present as inorganic iodide or as organic iodine in the form of thyroxine or diiodotyrosine or perhaps as triiodothyronine The distinction between iodine as iodide and iodine as hormone has lost some of its importance in the light of the previously mentioned research of Dvoskin[8]

The iodine stores in the body tissues have assumed new importance since the use of radioactive iodine in therapy and investigation for tissue absorption of radio iodine may lead to effects on other organs than the thyroid The total iodine content of the body generally is between 20 and 50 mg of which about 20 per cent resides in the thyroid gland In this gland iodine is many hundreds of times more concentrated than in other tissues except for other endocrine glands especially the gonads hypophysis adrenals, and parathyroids The mass of skeletal muscles is so large that its total iodine content is high in fact containing the major portion of the body iodine but the iodine concentration per gram of tissue is 1/1000 that of the thyroid The increased concentration of iodine in the endocrine glands will disappear after thyroidectomy whereas muscle and tissue iodine decrease only slightly This minor decrease in muscle iodine after thyroidectomy has been shown by Salter[10] to be due to loss of organically bound iodine from the muscles that contain both inorganic iodide and organic iodine

The thyroid itself under normal conditions has approximately 50 000 gamma per cent (50 mg per cent) of iodine

The iodine concentration in endocrine glands other than the thyroid is not large but may be of physiological importance The anterior pituitary contains from 80 to 190 gamma per cent[1] [13] whereas the posterior lobe contains considerably lower amounts

The iodine content of the adrenal cortex has been reported by Elmer and Scheps[14] as varying between 6 and 66 gamma per cent of dried tissue whereas the medullary content was found to be about 16 to 0 gamma per cent The ovaries contain relatively large amounts of iodine Maurer[15] Sturm and Bucholz[1] Carter[16] and Perkin and Brown[17] have all found concentrations of iodine in the ovary second only to those found in the thyroid itself The actual amounts found in various animals as well as in humans has been estimated to vary from 30 to 741 gamma per cent The testes have been found relatively low in iodine content[1]

Iodine Requirements and Iodine Balance

The iodine requirement of the organism has been studied by balance studies utilizing the usual techniques of measuring intake and output and by the indirect method of determining the minimal intake of iodine that will prevent goitrogenesis Both methods are subject to considerable experimental error balance studies deal with such minute amounts of iodine that technical errors readily occur, while histological changes may be late in appearance

The minimal daily requirement of iodine as estimated by balance studies lies between 15 and 25 micrograms according to Cole and Curtis[6] However Puppel and Curtis[3] as well as Scheffer[19] have found negative balances in some normal individuals receiving from 30 to 110 micrograms daily and Puppel and Curtis consider 50 to 100 micrograms as the minimal iodine need If one calculates the amount of iodine utilized daily in the form of thyroxine for the maintenance of normal thyroid function in myxedematous patients values ranging from 163 to 3[illegible]5 micrograms of iodine are realized[14, 3] The excess iodine over that found in balance studies is probably re synthesized into thyroid hormone Growth and increased total metabolism from whatever source augment the need for iodine Infants for instance have a larger iodine need when this is referred to either body weight or surface area

The Marine Cycle The Effect of Iodine Deficiency upon Thyroid Structure

Before modern microchemical techniques had become available for accurate balance studies Marine and his co workers[1, 2, 3, 4, 5, 6] had demonstrated most of the significant facts concerning the relation of the level of iodine intake to thyroid structure Marine found the following (1) iodine is necessary for normal thyroid function and morphology (2) iodine is rapidly taken up by the thyroid gland (3) the amount of iodine available determines the degree of hyperplasia in an inverse ratio (4) all hyperplasia of the thyroid is anatomically and chemical identical (5) thyrotoxicosis is regularly associated with thyroid hyperplasia with an inverse relation of iodine content to the degree of hyperplasia, (6) hyperplasia involutes to a colloid goiter or rarely results in exhaustion atrophy depending upon opportunities for a physiological rest as provided by iodine (see Table 1 and Fig 1)

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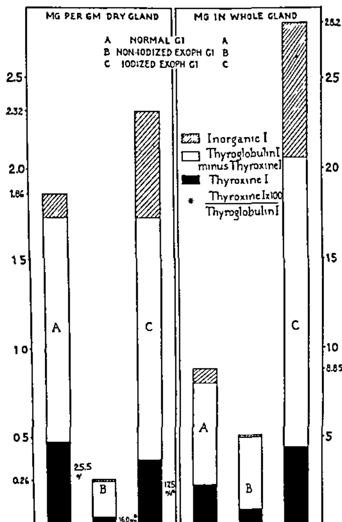


Fig 21 The average total iodine thyroxine iodine and inorganic iodine of 70 normal 44 non iodized and 70 iodized exophthalmic glands are compared in terms of mg per gm of dry gland and mg in the whole gland A is based on data of Leland and Foster and our own B is calculated from Wilson and Kendall From Gutman A B Benedict E M Baxter B and Palmer W W The effect of administration of iodine on the total iodine inorganic iodine and thyroxine content of the pathological thyroid gland Jour Biol Chem 1932 xcvii 303 24

TABLE I

THE RELATION OF IODINE TO THYROID STRUCTURE (THE MARINE CYCLE)
BASED ON DATA OF MARINE AND WILLIAMS

	Normal	*Early Hyperplasia*	*Moderate Hyperplasia*	*Marked Hyperplasia*	*Colloid Goiter*
Wt Fresh Gland gm /kg Body Wt	0 36 →	0 30 →	0 9 →	2 34	1.07
Conc of Iodine mg /gm fresh thyroid	0 78 →	0 14 →	0.08 →	0 0	0.46
Total Iodine in gland mg	1.42 →	0.44 →	0 54 →	0 29	3 23
					Exhaustion Atrophy

The only histological cycle which the thyroid follicle and its component cells are capable of undergoing is that described by Marine [7] and consists essentially in a progression from normal through varying degrees of hyperplasia to colloid goiter or exhaustion atrophy The colloid goiter represents a resting phase and is the closest approach to normal which a gland once hyperplastic can exhibit The colloid gland in turn may itself under appropriate conditions become hyperplastic and again become colloid or develop exhaustion atrophy In the latter condition, seen most frequently in endemic cretinism and in the late stages of hyperthyroidism there is loss of uniformity of the cells of the follicle wall with disintegration and desquamation of cells great irregularity and pyknosis of the nuclei with marked reduction of colloid Cell death reduces the size of the follicle with relative or absolute increase in the surrounding stroma

According to Marine s studies therefore the stimulus to hyperplasia arises whenever the amount of thyroid tissue is inadequate to supply sufficient hormone either as a result of reduced iodine intake by increased demands for thyroid hormone, or from partial thyroidectomy These changes are mediated through thyrotrophic stimulation

BLOOD IODINE

The level of total blood iodine measures both the iodine transported from the gastro intestinal tract to the thyroid gland and the hormonal iodine circulating from the gland to the tissues Kendall and Richardson [8] showed that normal blood contained iodine in a characteristic range This range has been found to lie between 5 and 20 gamma or

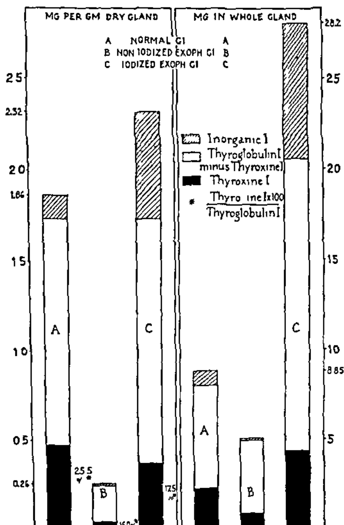


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micrograms per hundred cc of blood (1 gamma or microgram = 0.001 mg or 1/1000 mg) Temporary increases in these values to non physiological ranges will occur following the ingestion of iodides—for example Nelson and his associates[4] found concentrations up to 1500 micrograms when iodides were ingested by normal human subjects The relationship between plasma iodine concentration and iodine intake was linear The rate of disappearance of iodine from the plasma was also linear, so that basal values were attained within 72 hours

Early studies of blood iodine were largely confined to total iodine determination and required as much as 1 liter for satisfactory analysis Improvements in microchemical methods have resulted in lowering the amount of blood necessary for analysis to volumes ranging from 10 to 30 cc In addition as has been remarked by Bassett Coons, and Salter[29] Estimations of the apparent iodine concentration of the blood—have been falling steadily for two decades—however, the reported range of normal values has become rather stable in the past few years' The methods which are relatively exact but arduous require considerable skill in the technics of analytical chemistry The information obtained however is sufficiently valuable to warrant greater clinical use

A large experience in the application of total blood iodine analyses to clinical problems by Curtis and his co workers[30, 31] by Perkin and his associates[3, 33] and by Riggs and his collaborators[34] readily demonstrated the value of total blood iodine as a measure of thyroidal function Curtis[30, 31] however after thirteen years of experience with the estimation of whole blood iodine concluded that the basal metabolic rate was more reliable as a test of thyroidal activity than the level of unfractioned whole blood iodine Riggs[34] found a sharper contrast in the values for total blood iodine of normal persons and in patients with hyperthyroidism or myxedema His normal values were lower and less variable than previous studies ranging from 2 5 to 3 7 micrograms per 100 cc in subjects who had received no iodine for at least three weeks before the analysis or who had not had a diagnostic test using an iodine containing drug

Gley and Bourcet[3] were unable to remove iodine from the blood of dogs by dialysis and therefore concluded that plasma iodine was bound to protein Modern studies have confirmed their conclusion and have shown more exactly the nature of the various fractions of iodine found in the blood

Salter and his associates[29, 36] furthered knowledge of blood iodine fractions with chemical studies of the blood and correlated these studies with clinical material The protein-bound iodine in the plasma occurred

chiefly in the albumin fraction of the blood. Fluctuations in protein bound iodine were dependent upon thyroid activity. Fractionation of the protein bound iodine resulted in the finding of a low rather constant level of iodine due to diiodotyrosine and a higher variable level of iodine due to thyroxine. Total protein bound iodine varied largely with thyroxine secretion—it was high in thyrotoxicosis and low or absent in myxedema. Inorganic iodine as contrasted with protein bound iodine was found to be low and constant in value except following iodine ingestion. It was thus concluded and all subsequent observations have borne out this point that the measurement of protein bound iodine is of consider-

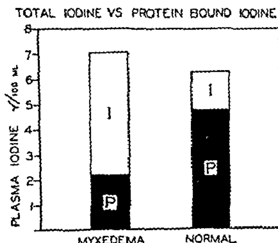


Fig. Values are given for inorganic I iodine and protein bound I iodine in the plasma of two individuals. Obviously unless the inorganic iodine is excluded the significant variations in P iodine may be masked. From Salter W T, Bassett A M and Sappington T S. Protein bound iodine in blood VI Its relation to thyroid function in 100 clinical cases. Am Jour Med Sci 1941 cciii 527 4

able value in the study of clinical thyroid physiology as it is an index of circulating thyroid hormone and may appropriately be called hormonal iodine (Figs 3 4).

In their cases of thyrotoxicosis and myxedema exact correlations between the basal metabolic rate, clinical evaluation and protein bound iodine levels in the serum were found in about two thirds of the patients. A critical analysis of the case histories however clearly indicates an even higher correlation between the protein bound serum iodine level and the state of thyroid function.

Riggs and his associates have contributed important studies on the effect of administered thyroid upon the protein bound iodine level in normal subjects and on the protein bound iodine concentration in the serum of patients with hyperthyroidism and myxedema.[37, 38, 39] In untreated myxedema the serum iodine was characteristically subnormal or absent; treatment with thyroid caused a linear elevation in the level of serum iodine in accordance with the dosage of thyroid, 65 mg. (1 gr.)

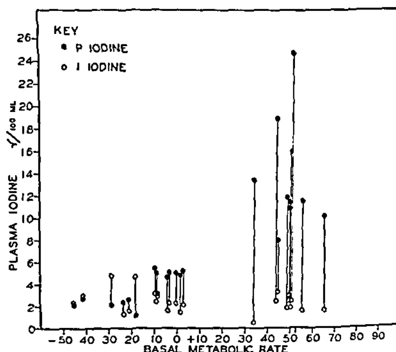


Fig. 23. In cases ranging from myxedema to marked hyperthyroidism the inorganic I iodine tends to remain constant although the protein bound P iodine rises as thyroid activity increases. From Bassett, A. M., Coons, A. H., and Salter, W. T.: Protein bound iodine in blood. V. Naturally occurring iodine fractions and their chemical behavior. Am. Jour. Med. Sci., 1941, ccii, 516-27.

elevating the serum iodine by 2 micrograms per 100 cc. The basal metabolic rate responded more slowly than the blood iodine levels to alteration in the thyroid state. In hyperthyroidism at least 95 per cent of all cases had elevation of the protein bound serum iodine. This elevation frequently declined with administration of iodides—occasionally to normal levels. Following radical subtotal thyroidectomy, low values often persisted permanently, associated with normal metabolic rates but with slight elevations in the serum cholesterol and some clinical evidence of

mild hypothyroidism The level of the serum iodine therefore was more sensitive than the basal metabolic rate in measuring thyroid hypo function

When desiccated thyroid was administered to normal subjects there was far less change in the metabolic rate and protein bound serum iodine than in myxedema The administration of 0 7 to . 0 gm (10 to 30 gr)

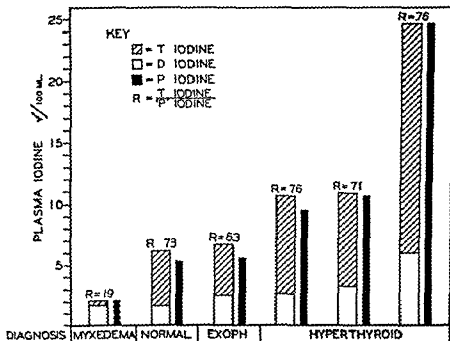


Fig 24 In cases ranging from myxedema to marked hyperthyroidism the absolute rise in protein bound P iodine is due largely to an elevated thyroxine like T fraction From Bassett A M Coons A H and Salter W T Protein bound iodine in blood V Naturally occurring iodine fractions and their chemical behavior Am Jour Med Sci 1941 ccii 516-27

of dried thyroid however caused abnormally high serum iodine levels an elevated basal metabolic rate and clinical signs of thyrotoxicosis Although the normal subject was resistant to thyroid once enough was given to raise the serum iodine the correlation between rises in that value and the basal metabolic rate was exactly the same as that in myxedematous patients *Two conclusions were drawn from this study* normal tissues are as sensitive to thyroid as myxedematous ones and the degradation of

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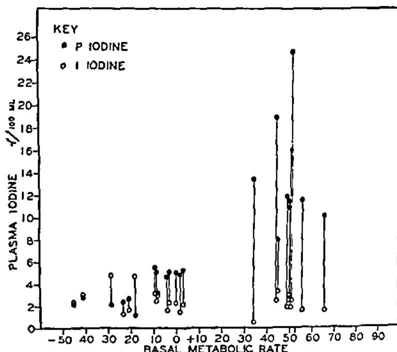


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normal iodine to inorganic iodine by the normal thyroid gland probably explains the tolerance of euthyroid subjects to large doses of thyroid. This paper[37] contains several instructive graphs showing the parallelism between precipitable serum iodine and basal metabolic rate when thyroid is administered (Figs. 25, 26, 27).

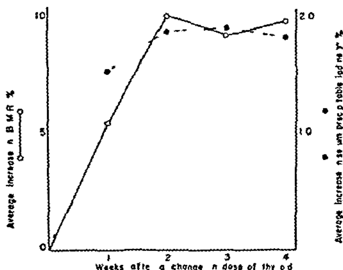


Fig. 26. Parallelism between the rate of change of serum precipitable iodine and of basal metabolic rate after an increase in thyroid dose. With increasing thyroid dosage there is almost no lag in the rise in the basal metabolism behind that of the serum iodine. This contrasts with the marked lag of basal metabolism behind serum iodine with abrupt discontinuance of thyroid medication. The increase in serum precipitable iodine or in basal metabolic rate occasioned by an increase in the dose of thyroid has been plotted against the time elapsed since the change in dose. The origin corresponds to the last value obtained while the previous dose was being administered. The points represent average values for increasing thyroid dosage in all 4 schizophrenic patients and for all increments of dose. *From* Riggs, D. S., Man, E. B. and Winkler, A. W.: Serum iodine of euthyroid subjects treated with desiccated thyroid. *Jour. Clin. Invest.* 1945, xxiv, 722-31.

Taurog and Chaikoff[40] investigated the effect of the level of daily iodine intake ranging from 1 to 480 micrograms upon the thyroxine and iodine content of the thyroid gland of rats and upon the total and protein bound iodine in the plasma. The level of the plasma protein bound iodine varied in accordance with the thyroxine content of the gland. Both were influenced by the iodine intake. An increase in iodine intake was followed by an increase in the total and thyroxine iodine

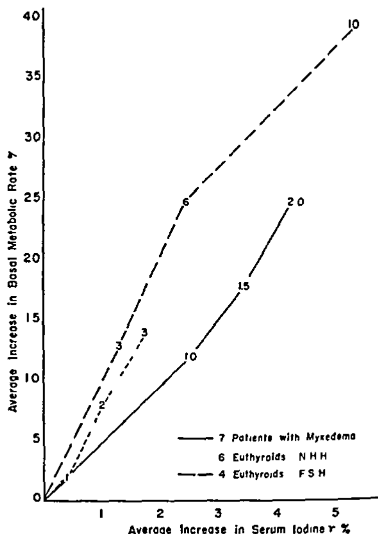


Fig 25 Relationship between the increase of serum precipitable iodine and of basal metabolic rate of myxedematous patients and of euthyroid subjects given desiccated thyroid The increase in basal metabolic rate above the average premedication level is plotted against the corresponding increase in serum precipitable iodine at various levels of thyroid dosage The dose in grains per day is indicated by the figures on the curves The curve for the patients with myxedema was calculated from data reported in a preceding paper Data from the 2 groups of euthyroid subjects reported here are plotted separately the New Haven Hospital patients being indicated by short dashes the Fairfield State Hospital patients by long dashes Each point is the average for all patients in a given group on a given dose of thyroid Note that the basal metabolic rate rises at least as much per unit increase in serum iodine in the euthyroid subjects as in those with myxedema but that a much larger dose of thyroid is required From Riggs D S, Man E B and Winkler A W Serum iodine of euthyroid subjects treated with desiccated thyroid Jour Clin Invest 1945 xxiv 722 31

observed up to certain levels of iodine intake beyond these levels increased intake failed to produce an elevation in the protein bound iodine (Fig 8)

Danowski and his associates[41 42] administered inorganic iodides in both massive and small amounts to human subjects and subsequently determined the effect of iodide upon the total protein bound and thyroxine iodine of the blood With daily doses of 3 gm of potassium iodide over periods as long as six months elevated levels of total and precipitable

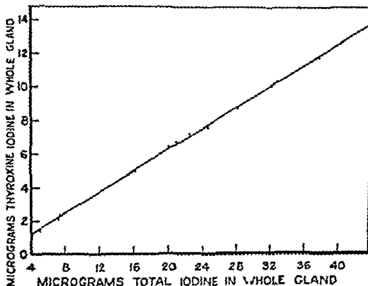


Fig 8 The relation of thyroxine iodine to total iodine in thyroid glands of rats that received varying amounts of iodine From Taurog A and Chaikoff I L The relation of the thyroxine content of the thyroid gland and of the level of protein-bound iodine of plasma to iodine intake Jour Biol Chem 1946 clxv 217 2

iodine occurred Total iodine levels up to oo micrograms per 100 cc occurred the protein bound iodine rose to values of 12 to 32 micrograms except in patients with myxedema The blood thyroxine levels however did not increase during iodide therapy so that it may be inferred that the protein bound iodine increment occurred in the non thyroxine portion—that is in iodinated tyrosine or a related unknown substance Obviously it is not possible in patients receiving large amounts of iodides for any considerable period to utilize the protein bound iodine as an index of circulating hormone

content of the thyroid gland to a point of maximal storage beyond which increments of ingested iodine had no further effect With maximal storage the iodine concentration in the gland was 10 000 times greater

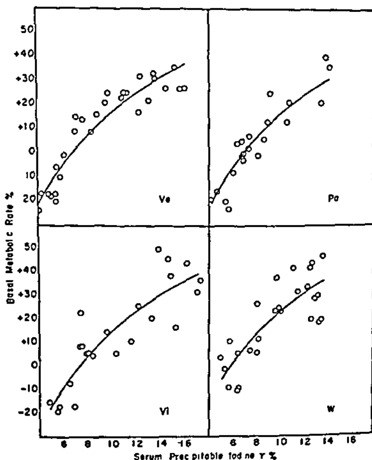


Fig 27 Correlation between serum precipitable iodine basal metabolic rate in 4 euthyroid schizophrenic patients The points represent individual determinations of serum precipitable iodine and corresponding values of basal metabolic rate Values determined after thyroid was discontinued are omitted for reasons discussed in the text The solid lines are the regression curves obtained when basal metabolic rate is assumed to be a function of the logarithm of the serum precipitable iodine From Riggs D S Man L B and Winkler A W Serum iodine of enthyroid subjects treated with desiccated thyroid Jour Clin Invest., 1945 xxiv 7 31

than in plasma The fraction of total iodine present as thyroxine in the thyroid gland remained relatively constant over the complete range of iodine intake Increased values for protein-bound iodine of plasma were

When a tracer dose of inorganic radio iodine is injected into a normal rat upon entering the thyroid gland it is quickly converted to organic iodine so that after 24 hours a maximum of 30 per cent of the injected radio iodine has been organically bound [43] In a gland made hyperplastic with propylthiouracil all the radio iodide entering the thyroid remains inorganic and a maximum of 9 per cent of the tracer material is taken up one hour after the injection

When labeled iodide is injected into normal rats the uptake of radio iodide by the thyroid is much slower than with tracer doses so that only 2 to 5 per cent is taken up after 6 hours but it is for the most part organically bound After one hour 50 per cent of the radio iodide in the thyroid is in the inorganic fraction this is in marked contrast to the large percentages of organic radio iodine in the gland following a tracer dose [43]

In the gland made hyperplastic with propylthiouracil the uptake of radio iodide whether as tracer or labeled is similar essentially all of the

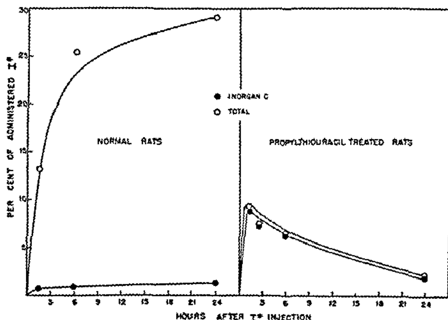


Fig 29 The uptake of a tracer dose of radioactive iodide by the thyroids of normal and propylthiouracil treated rats The latter received a diet containing 0 10 per cent propylthiouracil for 17 days From Taurog A Chaikoff I L and Feller D D The mechanism of iodine concentration by the thyroid gland its non-organic iodine binding capacity in the normal and propylthiouracil treated rats Jour Biol Chem 1947 clxxi 189-201

Chaikoff and his co-workers[43, 44] have studied further the metabolic significance of protein-bound plasma iodine by means of radioactive iodine They define protein-bound iodine as the iodine that is 'precipitated from plasma along with its proteins by such agents as tungstic acid zinc hydroxide, or acetic acid in the presence of heat and in addition cannot be freed from these proteins by simple washing' The chemical nature of this fraction needs much further clarification, as has been emphasized by Salter In Chaikoff s experiments in rats the protein bound iodine in plasma fell rapidly after thyroidectomy reaching minimal values on the third day The rate of incorporation of radio iodine into the protein-bound iodine fraction of the plasma was greatly depressed in these animals and significantly augmented in normal animals by thyrotrophin injection The conversion of injected radioactive inorganic iodine into protein bound iodine is thus proposed by Chaikoff as an index of thyroidal activity

The ten thousand fold concentration of iodine from the plasma by the thyroid gland is effected in the normal gland in part through organic binding of inorganic iodine to iodinated tyrosine and thyroxine as has been pointed out in previous discussion There is however, an additional and more significant mechanism of iodine concentration which is independent of hormonal synthesis and is referred to by Taurog Chaikoff and Feller[45] as the non-organic iodine concentrating mechanism of the thyroid In rats treated with propylthiouracil there is a complete block in the formation of organic iodine and yet the capacity of the hyperplastic glands of these animals for fixing iodine in non-organic form is greater than in the normal but is limited by the concentration of plasma iodide The iodine taken up by these glands is in the form of inorganic iodide and is not firmly bound to protein

Significant differences exist in the reaction of the normal and goitrous gland to radioactive iodine and in the response of either type of gland to tracer doses as compared with carrier or labeled doses of iodine In the tracer technique radioactivity is utilized in tracing the course of minute quantities of material through metabolic processes Labeled iodine designates ordinary iodine or iodide which is mixed with a small amount of radioactive iodine As Salter[7] has so well stated, labelled iodine is merely ordinary iodine in which one atom of (perhaps) every several million is tagged by its radioactivity Because these tagged atoms behave chemically precisely as do their fellows the investigator may assume safely that wherever he can detect one of these (perhaps) several million comrade atoms are present

become essential to the clinician and to the investigator of endocrine metabolism The ensuing explanation of the physical chemical principles involved in radioactive isotopes is based for the most part on the discussion by Buchta[4]

The modern concept of atomic structure is based upon the Bohr Rutherford theory of the atom Although the number of atoms is small the possible combinations of atoms of various elements are almost infinite at present for example over 500 000 known chemical compounds exist The undisturbed atom is electrically neutral because of the balanced arrangement of its constituents The atom consists of three particles the electron the proton and the neutron The electron represents the fundamental particle of negative electricity having a mass 1/2000 that of the neutron or proton The proton is the fundamental unit of positive electricity and has a charge that is the same in magnitude but opposite in direction to that of the electron The neutron with the same mass as the proton has no charge and is electrically neutral

Protons and neutrons make up the central core or nucleus of the atom Electrons revolve in an orbit about this nucleus The normal atom is electrically neutral because there are always as many electrons as there are protons in the nucleus Practically the entire weight or mass of the atom however resides in the nucleus The atom itself is largely space as Eddington has observed If all the atomic nuclei and electrons of the body were so compressed as to eliminate intra atomic and inter atomic space the resulting mass would be barely visible with a micro scope The atomic weight therefore is generally equal to the sum of the number of protons and neutrons in the atomic nucleus whereas the *atomic number corresponds to the number of electrons revolving about* the nucleus and hence is equal to the number of protons in the nucleus Thus hydrogen with one proton in the nucleus has an atomic number of one and an atomic weight of one since its nucleus contains only a single proton about which revolves a single electron Iodine with 53 pro tons has an atomic number of 53 and an atomic weight of 1 7 because it has 74 neutrons in addition to its protons The chemical properties of a compound are determined by the number and arrangement of elec trons about the nucleus but are independent of nuclear structure except when changes in the nucleus involve changes in the arrangement of electrons

Through physical measurements it has been found that all atoms of one element or chemical species do not have the same atomic weight Though these atoms all possess the same chemical properties because of an iden

radio iodide remaining inorganic at all time intervals Maximum uptakes of 10 per cent occur within 30 minutes with a steady decline thereafter so that after 26 hours only 0 5 per cent was found

These experiments with labeled iodides have shown that the goitrous gland of a rat has a much larger than normal capacity for fixing injected iodide in non organic form (Figs 29 and 30)

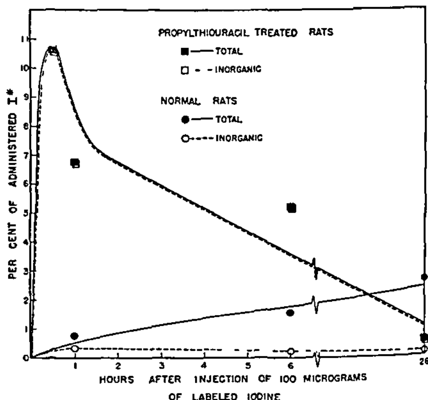


Fig 30 The uptake of 100γ of labeled iodide by the thyroids of normal and propyl thiouracil treated rats The latter received a diet containing 0 15 per cent propylthiour acil for 15 days From Taurog A Chaikoff I L and Feller D D The mechanism of iodine concentration by the thyroid gland its non organic iodine binding capacity in the normal and propylthiouracil treated rats Jour Biol Chem., 1947 clxxi 189 201

Radioactive Iodine

The use of radioactive iodine has introduced a new and important approach to the study of thyroid physiology and pathology An under standing of the nature and utility of radioactive or tagged atoms has

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The modern concept of atomic structure is based upon the Bohr Rutherford theory of the atom Although the number of atoms is small the possible combinations of atoms of various elements are almost infinite at present for example over 500 000 known chemical compounds exist The undisturbed atom is electrically neutral because of the balanced arrangement of its constituents The atom consists of three particles the electron the proton and the neutron The electron represents the fundamental particle of negative electricity having a mass 1/ 000 that of the neutron or proton The proton is the fundamental unit of positive electricity and has a charge that is the same in magnitude but opposite in direction to that of the electron The neutron with the same mass as the proton has no charge and is electrically neutral

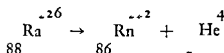
Protons and neutrons make up the central core or nucleus of the atom Electrons revolve in an orbit about this nucleus The normal atom is electrically neutral because there are always as many electrons as there are protons in the nucleus Practically the entire weight or mass of the atom however resides in the nucleus The atom itself is largely space as Eddington has observed If all the atomic nuclei and electrons of the body were so compressed as to eliminate intra atomic and inter atomic space the resulting mass would be barely visible with a micro scope The atomic weight therefore is generally equal to the sum of the number of protons and neutrons in the atomic nucleus whereas the atomic number corresponds to the number of electrons revolving about the nucleus and hence is equal to the number of protons in the nucleus Thus hydrogen with one proton in the nucleus has an atomic number of one and an atomic weight of one since its nucleus contains only a single proton about which revolves a single electron Iodine with 53 pro tons has an atomic number of 53 and an atomic weight of 127 because it has 74 neutrons in addition to its protons The chemical properties of a compound are determined by the number and arrangement of elec trons about the nucleus but are independent of nuclear structure except when changes in the nucleus involve changes in the arrangement of electrons

Through physical measurements it has been found that all atoms of one element or chemical species do not have the same atomic weight Though these atoms all possess the same chemical properties because of an iden-

tical electronic structure they vary somewhat in their atomic weights Atoms with the same nuclear charge and electronic structure but with different atomic weights are called isotopes Most elements have stable isotopes which are mixed in the same proportions wherever the elements occur

The naturally occurring proportions of isotopes can be varied by special chemical or physical methods and these new percentage mixtures of isotopes may be utilized for the study of metabolic transformations by tracing the route of the isotopic element Isotopes possessing radioactive properties lend themselves especially to this type of tracer study

Radioactivity involves changes in the atomic nucleus with natural transmutation These changes may occur through the disintegration of the nucleus and the emission of an alpha particle This alpha particle is the nucleus of the helium atom It has a high speed (12,000 to 18 000 miles per second) and large mass (over 7000 times that of an electron) The emission of the alpha particle reduces the remaining nucleus in charge and weight with the formation of two new elements thus



$$\overset{226}{\underset{88}{Ra}} \rightarrow \overset{222}{\underset{86}{Rn}} + \overset{4}{\underset{2}{He}}$$

The initial radium (Ra) atom had 88 protons and 138 neutrons with an atomic weight of 226 and disintegrated into Radon (Rn) with 86 protons and 136 neutrons and an atomic weight of 222 plus helium with 2 protons and 2 neutrons and an atomic weight of 4

Naturally occurring radioactive elements may disintegrate in a different fashion and emit beta particles or rays This can be illustrated by Radium E in which a neutron within its nucleus is converted into a proton and an electron The electron is ejected and is called a beta particle In this type of disintegration very short and penetrating gamma rays which are essentially x-rays may also be emitted The beta rays have extremely high velocity and are less than 1/7000 the mass of an alpha particle Since the rate of decay of radioactive elements is constant an element can be characterized by this rate As an example given a certain number of radium atoms one half would be disintegrated after 1600 years therefore the half life of radium is 1600 years The half lives of radioactive substances vary from a fraction of a second to millions of years Uranium has the longest half life of all and is most abundant

Radioactivity is thus seen to result from instability of atomic nuclei

The stability of the nucleus is determined by the number and arrangements of its fundamental particles. Artificial or induced radioactivity was discovered in 1934 by Joliot and Curie[47] who found that radioactivity could be induced by bombarding some of the common elements such as aluminum or magnesium with alpha particles. This radioactivity persisted for some time after the bombardment ceased. All the elements have subsequently been bombarded by alpha particles, neutrons, protons or deuterons (the nuclei of heavy hydrogen) through the use of the cyclotron, which tremendously accelerates positively charged ions, and the betatron, which accelerates electrons, of the uranium pile. Radioactive isotopes can be made for any of the elements of the periodic table.

At least six radioactive isotopes of iodine have been produced and even more of them described. However I^{131} (half life 8 days) and I^{130} (half life 12.6 hours) or a mixture of both has been utilized to the greatest extent. Both can be produced by bombardment of metallic tellurium with deuterons in the cyclotron. I^{131} is also a fragment of uranium disintegration and today is available from the uranium chain reacting pile. I^{131} has completely replaced I^{130} in clinical and research applications because of its advantageous half life and ready availability.

The disintegration of most elements with induced radioactivity involves the emission of a negative or a positive electron. The positive electron, known as the positron, is produced by the conversion of a proton into a neutron and then into a positron, which has the same mass as an electron but with an opposite charge. The positron is the positive charge of the proton. This phenomenon is peculiar to induced or artificial radioactivity and has not been observed in natural radioactivity. Gamma rays may accompany disintegrations involving electrons or positrons.

The amounts of radioactive isotopes produced by bombardment are so small that they must be measured by electronic methods sensitive to radiations. Radiations can be measured by their capacity to ionize air or some other gas imprisoned between charged plates. The rate of discharge of the plates is equivalent to the number of ions formed in the air or gas and that in turn to the quantity of impinging radiation. The Geiger counter, which detects gamma rays, is commonly utilized for the purpose of measuring irradiation from I^{131}. This instrument consists of a glass tube filled with gas at low pressure, with a fine wire along its axis and a thin metal coating on the inner wall to make it electrically conductive. A high voltage (1000 volts) is produced between the wire and the wall. When an ionizing beta or gamma ray passes through the tube, ions are formed in the gas and an electrical discharge occurs under the influence

of the high voltage The current is quickly suppressed so that a pulse of current is produced for each ionizing particle This current is amplified into audible clicks whose number per minute can be used to measure radioactivity The Geiger counter itself has several disadvantages as a clinical instrument It cannot be placed in close proximity to the neck since for accuracy it must survey the entire gland at a fixed distance of 6 to 12 inches with a resultant loss in geometric efficiency In addition it is insensitive detecting only 0 1 to 1 per cent of incident gamma rays from I^{131}

The scintillation counter which can be used to detect any ionizing event is a more sensitive detector of gamma rays than the Geiger counter and is now receiving clinical application[48, 49] The scintillation or fluorescent detector measures nuclear and atomic radiations by means of a phosphor and a photomultiplier tube A phosphor is a substance that emits or can be made to emit light without sensible heat The phosphor will transform a fraction of the energy from irradiation into light emission or scintillation The photomultiplier tube will transform the phosphor scintillation into an electrical pulse which can then be amplified and recorded on a scaler or counting rate meter Various types of organic and inorganic crystal phosphors may be utilized as scintillation crystals The photomultiplier tube multiplies the emitted light quanta from the crystal The scintillation counter has proved to be from 30 to 50 times as sensitive as the Geiger counter so that tracer doses as small as 5 to 10 microcuries may be employed

It should be understood that radioactive elements behave chemically and metabolically precisely as the natural elements providing the amount is so small as to be without biologic effects from the radiation itself thus allowing their use as a convenient method for studying physiological processes In tracer work the radiation itself must be so small that it does not affect the phenomena under investigation while this can be determined only by trial a knowledge of the tissue dose is helpful Marinelli and his associates[50] consider it desirable to express the dosage in terms of roentgens since that is the unit employed with x rays and radium Dosage data for x-rays radium and radon have been satisfactorily established and can be applied to any gamma ray emitting radioactive material enclosed in a sealed container and used in the same manner as radon As most radio isotopes are ingested or injected and eventually deposited in the various tissues however to obtain accurate dosage values one must know not only the physical factors of half life and radiation energy but also the physiological factors of uptake and excretion

Use of Radioactive Iodine in the Study of Thyroid Physiology

The application of radioactive iodine to thyroid investigation has been extensively mentioned in the preceding Parts as well as in the earlier sections of this Part. The thyroid, whether normal or pathological, cannot differentiate between ordinary and radioactive iodine; its response, uptake and retention of radioactive iodine has therefore served as a definite index of its reaction to ordinary iodide. The radioactive iodine utilized in the great bulk of reported investigations has been I^{131} with a half life of 8.0 days. This isotope emits chiefly beta rays whose action is limited to a few millimeters of tissue but with intense radiation within that area. Gamma rays are also emitted which ionize negligibly within the body but which are penetrating and can be measured by an externally placed gamma ray detector such as the Geiger or scintillation counter.

Hertz, Roberts and Evans[1] were the first to investigate thyroid function with radioactive iodine in animals. Hamilton and Soley[3] in the following year extended this method to normal and goitrous patients with and without thyrotoxicosis. These authors studied both the absorption and excretion of labeled iodine as well as the total and radioactive iodine content of the thyroid gland itself. Actual measurements of gamma ray emission were made by placing a Geiger counter over the thyroid gland and curves of iodine uptake were constructed. The urinary excretion of radio iodine in normal persons or in goitrous subjects with normal thyroid function was found to be similar. Patients with toxic nodular goiter had excretion rates that were the same as those in patients with toxic diffuse goiter. In patients with myxedema the renal excretion of radio iodine was much slower than in other patients but much greater amounts were excreted. Fecal excretion of radio iodine was low, not over 3 per cent except in one case where it was 11.5 per cent. A dose of radio iodine was detectable in the thyroid within twenty minutes after oral administration. Normal subjects excreted about 60 per cent of the dose in the urine over a 5 day period, most of it during the first 24 hours. The thyroid gland in hyperthyroid patients who had not previously received iodides took up iodine much more rapidly than the normal gland but was unable to retain this iodine as well as the euthyroid gland.

Hertz, Roberts and Salter[84] in 1942 found that the thyroid glands of patients with hyperthyroidism collected 80 per cent of administered radio iodine when the associated dose of sodium iodide was less than 2 mg. With larger accompanying doses of sodium iodide the percentage

collected was smaller Iodinized glands also collected smaller amounts of radio iodine

Rawson and his co workers[5] [56] *found that* in a patient with thiocyanate induced goiter *there was a small* percentage excretion of tracer amounts of radio-iodine *in the* urine whereas in a patient with thiouracil induced goiter all *of the* tracer dose was excreted Patients with untreated

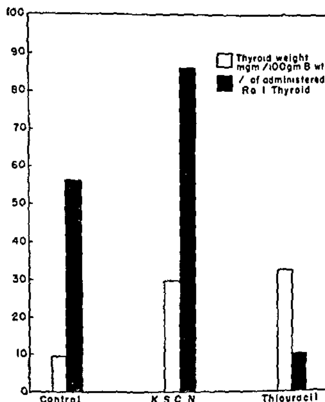


Fig 31 The collection of radioactive iodine by the thyroids of rats made goitrous by the administration *of potassium* thiocyanate and thiouracil The white columns represent the average thyroid weights *(mg 100 gm* body weight) The black columns represent *the average per cent collection of administered radioactive* iodine by the thyroids From Rawson R W and McArthur J W Radio iodine its use as a tool in the study of thyroid physiology *Jour Clin* Endocrinol 1947 vii 35 6,

thyrotoxicosis excreted *about* 15 per cent of administered radio iodine whereas *previous* administration of stable iodine resulted in large excretions (Fig 31 and 32)

Hamilton, Soley, and their co-workers[57] and Leblond[58] have studied the deposition *of radio* iodine in the thyroid gland by the radio autographic *technique* The former authors found that in goitrous glands

the element was concentrated in the most active portions In normal thyroid tissue the radioactive iodine was rather evenly distributed throughout the section In non toxic goiter with or without hypothyroidism the radio iodine was found in the cellular portions but not in the colloid In hyperplastic thyroid tissue the colloid had more radio iodine than the cells of the adjacent acini apparently owing to rapid excretion by the

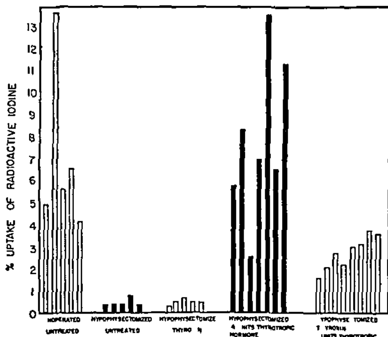


Fig 3 The effect of thyroxine on the response of the thyroid of hypophysectomized rats to thyrotropic hormone as indicated by the per cent uptake of administered radioactive iodine by the rats thyroids Each column represents the per cent uptake of radioactive iodine by a single animal s thyroid gland Twenty gamma of thyroxine were given daily for 10 days Thyrotropic hormone was given daily for the last 4 days of the experiment From Rawson R W and McArthur J W Radio iodine its use as a tool in the study of thyroid physiology Jour Clin Endocrinol, 1947 vii 235-63

hyperplastic cells Leblond s results differed somewhat from those of Hamilton and his group as he found that radio iodine administered orally to patients with non toxic or toxic diffuse goiters was rapidly deposited as diiodotyrosine or thyroxine in the colloid His observations would also indicate that the radio iodine passed through the epithelium

of the thyroid cell and was deposited in the colloid as diiodotyrosine

Keating and his associates [4] have utilized tracer amounts of radio-iodine in studies of the urinary excretion of radio iodine in various thyroid conditions The urinary excretion of radio iodine is technically simpler and more accurate than blood or tissue analysis and permits reason-

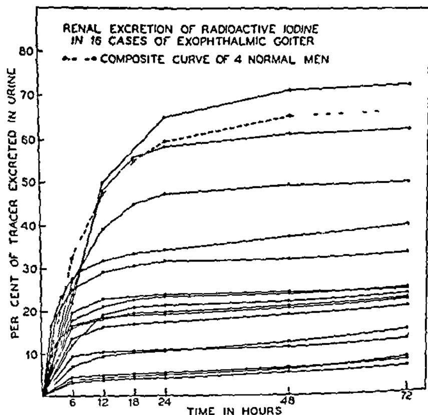


Fig 33 Urinary excretion of radio iodine in 16 cases of untreated exophthalmic goiter The cases varied widely in clinical severity basal metabolic rates and excretion of radio iodine Instead of reaching a plateau a slow and relatively constant excretion of radio iodine persists after the initial period of rapid excretion From Keating F R Jr Power M H Berkson J and Haines S F The urinary excretion of radio iodine in various thyroid states Jour Clin Invest 1947 xxvi 1138 51

ably accurate deductions regarding the absorption of radio iodine In euthyroid subjects from 45 to 75 per cent of the tracer was excreted in the urine within the first 48 hours reaching a plateau at about that time with a sharply rising excretion rate during the first 24 hours In myxedematous patients the rate of excretion was slower and the plateau was

not reached until after 4 or more days though in the end these patients excrete more radio iodine than euthyroid subjects Thyrotoxic individuals varied widely in their excretion of radio iodine In general their excretion rates were much less than normal but several cases with moderately severe thyrotoxicosis had excretion rates that were indistinguishable from the normal Quimby and McCune[60] studied radio iodine uptake in the thyroids of children by direct measurements over the gland after the method of Hamilton and Soley They found large

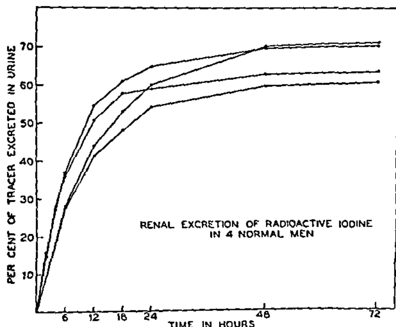


Fig 34 Urinary excretion of radio iodine in 4 normal men The form of the curves suggests an exponential function From Keating F R., Jr., Power M H Berdson J and Haines S F The urinary excretion of radio-iodine in various thyroid states Jour Clin Invest 194 xxvi 1138 5

uptakes in hyperthyroidism and low uptakes in hypothyroidism Some normal glands however had uptakes comparable to those found in myxedema The range of uptake and excretion in euthyroidism thyrotoxicosis and myxedema is such that the thyrotoxic gland may respond as a normal gland with average uptake while the action of the normal gland may be like that of the hypofunctioning gland of myxedema with minimal uptake of radio iodine (Figs 33 34 35 36)

The measurement of the excretion of radio iodine as a diagnostic method has been increasingly replaced by determination of the radio iodine uptake as more accurate methods have become available The measurement of uptake is particularly useful since it precisely determines the amount of isotope in the thyroid gland and eliminates errors due to inaccurate urine collection or adventitious temporary storage of radio

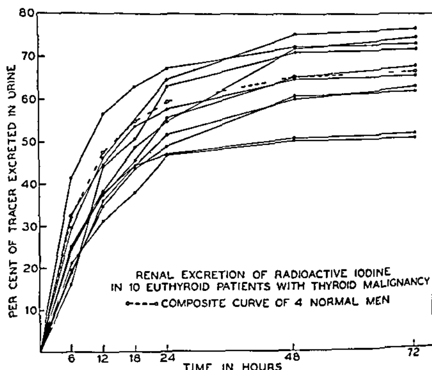


Fig 35 Urinary excretion of radio iodine in 10 euthyroid patients who had low grade thyroid malignant lesions The composite curve of the normal men is included for comparison Individual curves vary not only in the plateau that is reached but also in the time required to reach it From Keating F R Jr Power M H Berdson J and Haines S F The urinary excretion of radio iodine in various thyroid states Jour Clin Invest 1947 xxvi 1138 51

iodine in extrathyroidal tissues Radio-iodine uptake by the thyroid gland has been measured in our clinic by the four tube method devised by Freedberg [61] single Geiger tubes however, have yielded results that are no less accurate for clinical purposes [c] A sensitive method of measuring uptake is a decided advantage since the values obtained will show less overlap in euthyroid hypothyroid and hyperthyroid subjects

Keating and his associates[83] have employed four methods for measuring radio iodine accumulation in the human thyroid gland (1) measurement of the quantity of radio iodine excreted in urine within 48 hours after its administration (2) determination of extrarenal disposal rate from analysis of the curve of urinary radio iodine excretion (3) in vivo measurement of the quantity of radio iodine accumulated in the thyroid

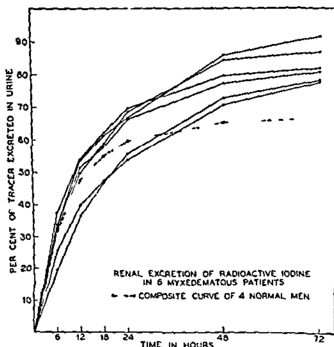


Fig 36 Urinary excretion of radio iodine in 6 patients who had myxedema The composite curve of the normal men is included for comparison Not only does more radio-iodine appear in the urine in myxedema but a much longer time is required to reach a plateau From Keating F R Jr Power M H Berkson J and Haines S F The urinary excretion of radio iodine in various thyroid states Jour Clin Invest 1947 xxvi 1138 51

24 hours after administration and (4) determination of an in vivo accumulation rate All four methods proved equally sensitive in studies of 790 patients with various conditions Extrarenal disposal rate provided the clearest picture of the state of radio-iodine function particularly in situations complicated by altered renal function In vivo observations provided more accurate information in the presence of reduced or absent

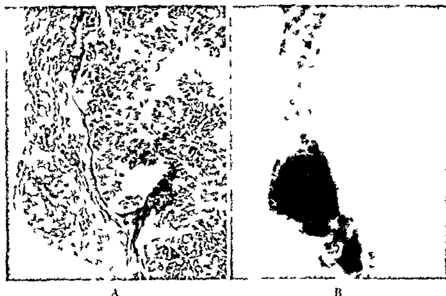
iodine accumulation than did urinary observations, but in other circumstances they were less efficient possibly owing to the intrinsic inaccuracies of in vivo measurements Determination of 48 hour urinary excretion proved a less specific measure of uncomplicated hyperthyroidism than the others and in some conditions it provided inexact and misleading information It was however the simplest and least expensive of the procedures employed

Measurement of radio iodine accumulation by any one of these methods was found highly efficient in separating more than 90 per cent of cases of exophthalmic goiter from normals Radio-iodine accumulation was significantly increased in the thyrotoxic group and strikingly reduced in patients with myxedema Discrepant results, however, were obtained in several conditions Some euthyroid patients with nodular goiter colloid goiter hyperplastic thyroid nodules and thyroid hyperplasia from antithyroidal drugs showed significant elevations of radio iodine accumulation Notable depression of radio iodine accumulation also occurred in many conditions unaccompanied by clinical hypothyroidism These included Addison s disease acute diffuse thyroiditis and Riedel s thyroiditis It was also observed for weeks to months following ingestion of inorganic iodine desiccated thyroid, and other organic iodine-containing compounds such as iodoalphionic acid (Priodax) used in roentgenography Antithyroidal goitrogenic drugs also interfered with radio iodine accumulation Normal values for radio iodine accumulation were observed in most cases of non toxic nodular goiter in about half of those with toxic nodular goiter in a few of exophthalmic goiter, and in some of myxedema Patients with Hashimoto s thyroiditis and associated clinical myxedema characteristically had normal values for radio iodine accumulation

The use of radio iodine in the study of hormone synthesis pituitary thyroid interrelations and the mode of action and assay of anti thyroidal goitrogens has been extensively described in the preceding Parts In addition radio iodine has been utilized to study the hormonal function of benign and malignant thyroid neoplasms Thyroxine labeled with radio iodine has been used by Gross and Leblond [64] to study the distribution of the hormone in various organs and tissues Radioactive thyroxine was injected into young female rats and its distribution at 2 and 4 hours in various organs measured The radioactive thyroxine quickly left the circulating blood and about one half was detectable in the gastro intestinal tract liver and pancreas within 2 hours The kidneys lungs adrenals ovaries and lymphatic tissue also showed significant amounts At

the end of 4 hours 80 per cent of the thyroxine was in the feces but the liver kidneys adrenals ovaries and lymphatic organs maintained their concentration The entrance to the gastro intestinal tract was by way of the liver and bile The pituitary gland and hypothalamus showed little or no fixation in contrast to previously reported results in rabbits

Fig 37



A B

(A) A section of low-grade papillary adenocarcinoma with clear demarcation of tumor from adjacent non-cancerous thyroid tissue At lower left is an oval area which histologically is a colloid adenoma

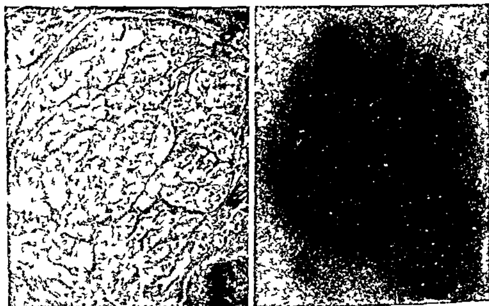
(B) The corresponding radio autograph which shows that the areas of darkening outline the non cancerous thyroid tissue There is no darkening of the plate where it was in contact with the tumor itself The oval area rich in colloid is shown to have picked up a relatively large amount of isotope as judged by degree of darkening

From Marinelli L D Foote F W Hill R F and Hocker A R Retention of radioactive iodine in thyroid carcinomas histopathologic and radioautographic studies Am Jour Roentgenol and Rad Therap 1947 LVIII 17 32

The functional capacity of various types of benign and malignant tumors of the thyroid has been measured by their uptake of radioactive iodine Radio autography and direct counts over the thyroid gland and metastatic areas have served as the two techniques of investigation Hamilton Soley and Eichorn[65] found no deposition of iodine in thyroid

carcinoma by means of radio-autography However Frantz, Ball Keston and Palmer[66] Marinelli and his group[67 68 69] Cope and his co-workers,[70 71] and Leblond and his associates[7 73] have demonstrated that the iodine uptake of a malignant tumor depends upon the nature of the tumor The more differentiated carcinomas, especially the malignant adenomas, have a high uptake of radioactive iodine either in the thyroid itself or in distant metastases The less differentiated tumors collect radio-

Fig 38



A B

(A) A medium magnification of a solid alveolar adenocarcinoma

(B) The corresponding radio autograph showing marked retention of radioactive iodine by the tumor tissue

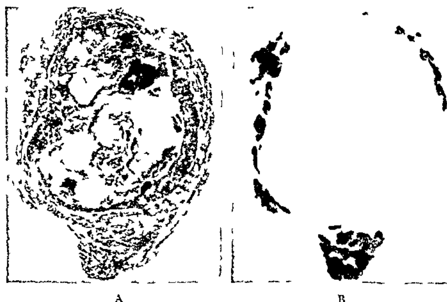
From Marinelli L D Foote F W Hill R F and Hocker A R Retention of radioactive iodine in thyroid carcinomas histopathologic and radioautographic studies Am Jour Roentgenol, and Rad Therap 1947 LVIII 17 3

iodine in much smaller amounts or not at all About 15 per cent of all malignant tumors may be expected to take up radio iodine in some degree The benign metastasizing goiter has the highest uptake and is most susceptible to therapy with radio iodine (Figs 37 38 39)

Cope[71] by means of radioactive iodine was able definitely to establish the existence of hyperfunctioning single adenoma of the thyroid through

an avidity for tracer doses of radioactive iodine comparable to that found in ordinary toxic goiter

Fig 39



(A) A Hurthle cell adenocarcinoma occupies the central portion of this section and is surrounded almost entirely by a rim of adjacent thyroid tissue The tumor itself is partly hemorrhagic and broken down

(B) The corresponding radio-autograph fails to show the deposit of any isotope in the tumor itself

From Marinelli L D Foote F W Hill R F and Hocker A R Retention of radioactive iodine in thyroid carcinomas histopathologic and radioautographic studies Am Jour Roentgenol and Rad Therap 1947 lviii 17 32

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PART V

CLASSIFICATION OF DISEASES OF THE THYROID METHODS OF EXAMINATION OF PATIENTS WITH THYROID DISEASE

Classification of Diseases of the Thyroid

A perfect classification of disorders of the thyroid is not yet possible owing to the lack of sufficient knowledge with respect to the etiology physiology and pathology of most thyroid abnormalities The term goiter denotes enlargement of the thyroid gland whether or not the enlargement is diffuse or nodular benign or malignant or attended with symptoms and signs of increased or decreased function A simple and useful clinical classification of thyroid disease should include only those qualifying terms that are justified by the clinical picture of a given thyroid disorder The following classification has been used in our clinic and is in accord with that recommended by the American Association for the Study of Goiter

1 Non toxic diffuse goiter (iodine deficiency goiter endemic and sporadic)
2 Non toxic nodular goiter
3 Toxic diffuse goiter (exophthalmic goiter Graves disease thyrotoxicosis)
4 Toxic nodular goiter (toxic adenoma)
5 Thyroiditis (inflammatory disease of the thyroid)
   (a) acute suppurative and non suppurative
   (b) subacute or pseudotuberculous
   (c) chronic
      (1) lymphadenoid goiter (Hashimoto)
      (2) Riedel s struma
      (3) tuberculosis
      (4) syphilis
      (5) actinomycosis

(6) Echinococcus disease
(7) Chagas' disease
(8) amyloid disease
6 Thyroid deficiency
(a) *cretinism*
(1) endemic
(2) sporadic
(b) myxedema
(1) primary
(a) idiopathic
(b) following antithyroidal drugs radioactive iodine therapy, and thyroidectomy
(2) secondary to hypopituitarism
7 Neoplasms of the thyroid
(a) benign
(1) papilliferous adenoma or papillary cystadenoma
(2) non-papilliferous or simple adenoma
(a) the embryonal adenoma
(b) the fetal adenoma
(c) the simple adenoma
(d) the colloid adenoma
(e) the Hurthle cell adenoma
(b) malignant
(1) low malignancy
angioinvasive tumors
(a) adenoma
(b) malignant papillary cystadenoma
(2) moderate malignancy
adenocarcinoma
(a) papillary
(b) alveolar or solid
(c) Hurthle cell
(3) high malignancy
(a) carcinoma
(1) small cell (carcinoma simplex)
(2) giant cell
(3) epidermoid
(b) sarcoma
(1) fibrosarcoma
(2) lymphosarcoma

8 Thyroid anomalies
(a) lingual goiter
(b) lateral aberrant thyroid
(c) thyroglossal cysts

METHODS OF EXAMINATION

The examination of patients with possible thyroid disease should be systematic and as in all patients should proceed from the history and physical examination to laboratory determinations of both general and specific character The features of the history that are of diagnostic usefulness may be considered in three groups
(1) symptoms of hyperfunction
(2) symptoms of hypofunction
(3) symptoms produced in surrounding structures by the goiter
In addition familial and environmental factors are frequently pertinent

The symptoms of hyperfunction are primarily due to excessive secretion of thyroid hormone These commonly present themselves as nervousness palpitation tremor weight loss dyspnea weakness increased sweating increased appetite, and diarrhea A fuller account of the symptomatology of thyrotoxicosis will be given in the Part on Toxic Diffuse Goiter Hypofunction of the thyroid manifests itself chiefly by thermophobia decreased sweating hypersomnia myxedematous swelling of the skin and face bradycardia slowness of cerebration and speech gain in weight and hoarseness Finally the thyroid enlargement may be painful and tender when it is the site of acute inflammatory disease or it may produce local pressure symptoms upon the trachea esophagus neck veins or the recurrent laryngeal nerves While excessive or deficient secretion of the thyroid hormone can generally be measured by its effect on heat production through the estimation of the metabolic rate only part of the symptoms of hyperfunction or hypofunction are related to the calorigenic activity of the thyroid Means and Lerman[1] have pointed out the extent to which the symptoms of thyroid dysfunction may be explained on the basis of alterations in the metabolic rate Marked hypermetabolism induced by dinitrophenol for example produces none of the symptoms of thyrotoxicosis Dodds and Robertson produced basal metabolic levels of 20 to 30 per cent by the administration of dinitro o cresol in patients with myxedema without any change in the clinical picture An elevated basal metabolic rate from non thyrogenous causes will not induce increased warmth or sweating or indeed tachycardia Even persons who are normal in every respect may have low metabolic

rates and yet not show any symptoms or signs of hypothyroidism

The physical examination of the patient should be supplemented by search for those features that are indicative of thyroid disorders. The general appearance and manner of the patient will vary from the overactive exuberant restlessness of the thyrotoxic individual to the slow, deliberate and phlegmatic character of the patient with myxedema. Stature is of importance in juvenile patients since there may be an increased rate of growth in hyperthyroidism or cretinous dwarfism in hypothyroidism. The nutritional status may also reflect thyroid dysfunction as well as vitamin deficiencies resulting from such dysfunction. Marked obesity rarely occurs with myxedema but hyperthyroidism not infrequently produces emaciation.

The facies in hyperthyroidism or myxedema are usually characteristic, showing in the former instance flushed shiny and moist skin with bright staring eyes and leanness of the face. In myxedema there is a general puffiness of the face with thickened and blunted features having a yellowish pallor; the eyelids are puffy and the lips thickened; malar flush may be observed. The hair is fine and glistening in hyperthyroidism and may be prematurely grey, in hypothyroid states the hair is dry, coarse and brittle, it is usually sparse over the temporal regions of the scalp and the outer portions of the eyebrows; the beard grows slowly.

The skin generally is pink, warm and moist in hyperthyroidism whereas it is dry, scaly, thickened, pale, and cold in myxedema; the thickening is most noticeable over the extensor surfaces; subcutaneous fat pads are usually present over the wrists and in the supraclavicular and and suprascapular areas.

The tongue on extension shows a fine tremor in hyperthyroidism; it may be otherwise normal but frequently presents features indicative of deficiency of the B vitamins. In myxedema the tongue is large, overfilling the mouth, is heavily coated, and shows dental impressions along its periphery on extension. The voice is low pitched, guttural and hoarse in myxedema with slow and halting speech but in thyrotoxicosis the speech may be rapid and dissilient.

Eye changes are frequently associated with altered thyroid function but are not in themselves indicative of the state of thyroid function. The changes that are commonly noted comprise exophthalmos, widened palpebral fissures, ocular palsies of varying degrees, lid lag, fatty or myxedematous swelling of the upper and lower lids as well as injection and chemosis of the conjunctivae and corneal ulcers. The ocular syndromes associated with toxic goiter will be considered more elaborately

in the discussion of that disease Exophthalmos may be simulated by widening of the palpebral fissures and is best evaluated clinically by observation of the eyeball after gentle closure of the eyelids This also permits detection of incomplete closure of the palpebral aperture such as may occur during sleep in the exophthalmic patient The exact degree of exophthalmos is readily measured with the Hurthle exophthalmometer By means of mirrors this instrument can determine with considerable accuracy the degree of eyeball protrusion through measurement of the distance from the deepest part of the lateral wall of the bony orbit at or just below the frontozygmatic junction to the point of greatest convexity of the cornea

Cardiovascular changes are noteworthy when thyroid function is altered In hyperthyroidism the heart is overactive and may be dilated the rate is increased the pulse pressure widened by an increase in systolic pressure as well as a decreased diastolic pressure physiological systolic murmurs are frequent over the pulmonic and mitral areas the snapping and accentuated first sound at the apex with tachycardia may simulate a short presystolic murmur paroxysmal auricular fibrillation may be present In myxedema the heart is usually enlarged the sounds are quiet and the rate is decreased, murmurs and arrhythmias are usually absent

Neuromuscular manifestations occur frequently in thyrotoxicosis These include the usual fine rapid tremor of the extremities as well as various myopathies and muscular weakness In myxedema there may be slowness of cerebration and muscular weakness Toxic psychoses may occur in both conditions

Finally the thyroid itself should be carefully examined by inspection palpation and ausculation For inspection of the thyroid adequate illumination and complete exposure of the neck are essential The patient should be comfortably seated with the chin slightly extended and the neck muscles relaxed The thyroid region should be viewed both from in front and from the sides Normally except in thin individuals the contours of the thyroid are not apparent In pathological states various degrees of enlargement may be visible The degree of symmetry the presence of nodules or masses and enlargement of neighboring lymph glands may be readily discernible Lesser degrees of enlargement and small or deeply placed nodules may become perceptible only during swallowing This is best accomplished by having the patient swallow small mouthfuls of water while the thyroid region is under inspection In addition one should note scars telangiectacies distended neck veins and increased or abnormal pulsations

Observation of the effect of deglutition on the position and mobility of the goitrous thyroid is of great diagnostic value Nodular and diffusely enlarged thyroid glands will ordinarily move upward during swallowing This arises from the close relation between the thyroid and the larynx and the trachea which are pulled upward with swallowing With infiltrative lesions that have extended beyond the thyroid capsule and adhered to surrounding structures the upward movement on deglutition may be lost Very large goiters may appear fixed, but careful examination during swallowing will usually reveal slight movement of the larynx underneath the mass Other swellings not connected with the thyroid but attached to or arising from the larynx and trachea may also exhibit upward motion during the act of swallowing These will usually consist of rare chondromatous tumors arising from the outer surface of the larynx or more rarely lymph nodes that have become adherent to larynx or trachea Occasionally fibromas or sebaceous cysts may simulate goiter especially when there is upward movement in swallowing because of attachment to the larynx or trachea

For palpation of the thyroid satisfactory relaxation of the neck muscles may be obtained by seating the patient in a chair with high and straight back support although this is not essential in most patients Slight flexion of the neck will secure adequate relaxation of the neck muscles Because of the helpful information obtained through deglutition a glass of water should be at hand for the patient s use Though many authorities prefer to palpate the gland while standing behind the patient our experience has indicated that adequate palpation may be carried out by sitting in front of the patient Palpation yields information regarding the size and general contour of the gland its consistency, symmetry, degree of surface smoothness or nodularity, the presence of thrills and tracheal displacement A special palpatory technique is used to determine the presence of deeply placed nodules and more clearly to outline the lateral borders of the gland In this method the patient first holds a small amount of water in the mouth until requested to swallow The examiner then displaces the trachea with the thumb of one hand and grasps the opposite thyroid region with the fingers and the thumb of the other hand the latter thumb lying along the anterior border of the sternocleidomastoid muscle and the fingers approximately posterior to the thyroid lobe The patient is then asked to swallow and as swallowing occurs the thumb and fingers are brought together with the thyroid lobe and its contents pressed firmly between Pressure is constantly maintained by the opposite thumb to displace the trachea in such a manner as to force

the lobe that is undergoing examination into the examiner's grasp This maneuver is repeated with the other side Many swallows may be necessary before the examination is completed and the examiner is satisfied regarding the presence or absence of nodules their degree of mobility and their relation to deglutition In addition direct palpation of the thyroid may be achieved by displacement of the medial border of the sternocleidomastoid muscle and by fingering the surface of the exposed lobe In some patients the neck muscles are better relaxed when the patient is recumbent with the head of the table raised

The normal thyroid gland cannot be felt except in thin persons when it may be barely outlined as a thin layer of tissue slightly firmer in consistency than the overlying soft tissues Thyroid size can be roughly estimated as there are no really accurate clinical methods of determining its size or weight The size of discrete nodules may be approximated and stated in metric measurement Diffuse enlargement is ordinarily stated in relation to the size of the normal gland

The consistency of the goitrous gland may vary from the soft doughy character of the small colloid gland to the stony hardness of chronic thyroiditis calcification or malignancy Tenderness is present only in acute thyroiditis or following sudden hemorrhage in a thyroid cyst The hyperplastic gland of Graves disease is firm rubbery and well delineated usually with palpable thrills over the superior poles Following iodinization the hyperplastic gland hardens in consistency and the lobes may become so sharply marked as to simulate nodules Nodular goiters also vary greatly in consistency from soft cystic masses which merge into surrounding thyroid parenchyma to firm discrete swellings such as are seen with benign or malignant tumors

Symmetrical enlargement is the rule with early colloid goiters in Graves disease and in certain types of chronic thyroiditis whereas benign and malignant nodular goiters are usually asymmetrical This asymmetry frequently leads to displacement and compression of the trachea The displacement is discernible on physical examination but anteroposterior compression can be determined only by roentgenography

Palpable thrills are frequent in thyrotoxicosis and may be occasionally present in large cystic masses containing dilated blood vessels The thrill is the palpatory equivalent of systolic or systolic and diastolic murmurs which may be audible by stethoscopy over the upper poles of the thyroid gland Thrills and murmurs must be differentiated from those trans-

mitted along the carotid vessels If present they constitute supporting evidence of thyroid hyperfunction

Finally, laryngoscopic examination of the vocal cords is indicated in all thyroid patients with hoarseness voice changes stridor and dyspnea In all those patients who may be subjected to thyroidectomy, inspection of the vocal cords is obligatory, since the presence of vocal cord palsy will influence the decision on operation, the type of anesthesia, and the scope of the operation itself The need for laryngoscopy under these circumstances arises from the close anatomical relation of the recurrent laryngeal and superior laryngeal nerves to the posterior surface of the gland While thyroidectomy is the more frequent cause of injury to these nerves, thyroid disease itself may be responsible through pressure stretching, or actual infiltration of the nerves Any type of thyroid disease may cause such involvement of the nerves but malignancy and thyroiditis are more likely to do so

Roentgenographic Examination

This method of examination aids in the demonstration of the following (1) tracheal displacement compression and softening, (2) esophageal displacement, (3) calcification within the thyroid, (4) intrathoracic extensions of a cervical goiter or aberrant thyroid nodules placed within the thorax, (5) cardiac changes induced by thyrotoxicosis or hypothyroidism (6) alterations in bone associated with thyroid disease

Both anteroposterior and oblique roentgenograms are essential for the evaluations of tracheal displacement and compression caused by thyroid pathology Lateral displacement of the trachea will appear in anteroposterior view whereas compression will be more readily exhibited by an oblique view Tracheal malacia or softening of the tracheal rings may be best observed fluoroscopically by the Valsalva experiment forced expiration with the nose and mouth closed produces visible distention of the trachea at the area of softening Such softening may lead to tracheal collapse during operation and is therefore an indication for intratracheal anesthesia

Dysphagia is rarely produced by goiter, but esophageal displacement and narrowing are not uncommonly found with nodules situated between the trachea and esophagus or with intrathoracic goiter Such alterations are readily demonstrated by anteroposterior and lateral views taken during the swallowing of barium

Hardness of a thyroid nodule may be due to calcification and this can

be demonstrated only by roentgenography As a rule thyroid malignancy does not show calcification

The presence size and extent of intrathoracic or substernal goiters can be realized only by adequate roentgenologic examination of the upper thorax utilizing anteroposterior oblique and lateral views with associated barium swallows to visualize the full effect on adjacent structures

Roentgenography is also important in demonstrating the effects of increased or decreased thyroid function upon heart size and shape rhythm and amplitude of contraction In thyrotoxicosis there is usually a dilated heart with rapid forceful contraction with striking overactivity and occasionally paroxysmal fibrillation There may also be dilatation of the pulmonary conus In myxedema the heart is enlarged in all diameters assuming a pear shape with slow regular rhythm and feeble amplitude of contraction A small pericardial effusion is frequently present

Alterations in bone structure may occur in thyroid disease Long standing thyrotoxicosis in elderly patients leads to extensive osteoporosis with pathological fractures particularly in the spine In juvenile hypothyroidism on the other hand epiphyseal development is delayed and the bone age retarded Periodic roentgenographic examination of the epiphyses is particularly important in this group of patients in observing the effect of therapy with thyroid substance

Special Diagnostic Procedures in Thyroid Disease

The definitive evaluation of alterations in thyroid function depends ultimately on the employment of special laboratory procedures which have proved dependable when properly carried out and critically interpreted The special procedures include the following

(1) the measurement of the basal metabolism
( ) the determination of the protein bound or serum precipitable iodine
(3) the measurement of the uptake and excretion of a tracer dose of radioactive iodine
(4) the determination of the cholesterol content of the blood
(5) the measurement of the arm to tongue circulation time
(6) electrocardiography

Basal Metabolism in Thyroid Disease

The measurement of the basal metabolism has become the starting point in the laboratory investigation of thyroid function and its value has been repeatedly affirmed in the diagnosis of thyrotoxicosis and myx

edema 'Basal metabolism actually represents the rate at which oxygen is consumed by an individual lying quietly in the morning, 12 to 14 hours after the last ingestion of food From the oxygen consumption one can readily calculate the caloric production with a maximum error of 3 5 per cent a degree of error of no clinical significance The calculations rest upon the value of oxygen in terms of calories with an assumed respiratory quotient of 0 82, 1 liter of oxygen at this respiratory quotient representing caloric values of between 5 047 and 4 485 depending upon whether carbohydrate, fat, or protein is being consumed the difference being slight so long as oxygen is measured The measurement of carbon dioxide as a yardstick of metabolism introduces errors up to 33 per cent since 1 liter of carbon dioxide represents 5 047 calories when pure carbohydrate is burned, but 6 694 calories in the oxidation of fat Thus all modern metabolism machines measure oxygen consumption in a given short unit of time by methods of considerable accuracy All these methods depend upon the measurement of oxygen absorption by the subject in a closed system with the removal of expired carbon dioxide by soda lime The circulation through the closed system is directed either by simple one-way valves or by an electric motor The latter is not necessary for ease of breathing but does allow the use of tubing of small diameter

The basal metabolism in health varies with age sex and size and depends for its usefulness on correlation with normal standards of reference The effect of age upon the basal metabolism is well established not only by the study of various age groups but even better, by repeated determination on the same subject at yearly intervals From the age of [illegible] to over 70 there is a progressive decline in the basal metabolism During the first year of life there is a sharp rise to the peak values of infancy and the growth period followed by a gradual decline during adult life[3] The effect of sex upon the basal metabolism is slight but definite females having a lower metabolism in ranges of from 4 to 10 per cent depending upon age In pregnancy, there is a gradual rise of 10 to [illegible]0 per cent in the basal metabolism especially in the last trimester This has been ascribed to the fetal participation in the total metabolism of the mother[4,5] Marine Cipra and Hunt[6] however feel that there is actual thyroid hyperactivity during pregnancy and this is validated by the finding of moderate elevations in the level of the protein bound serum iodine in the pregnant woman[7] In this instance however, it is impossible to assess the fetal contribution of thyroid hormone to the maternal circulation

Basal metabolism can be measured accurately in any patient in terms of total oxygen consumption for any short period of time This oxygen consumption can with equal accuracy be connected to heat production or caloric output The figure thus obtained when expressed as calories per unit of time will not however by itself indicate whether the individual is consuming oxygen at a normal increased or decreased rate It is therefore necessary to relate the caloric output to a factor that is more significant than age and sex namely body size This may be accomplished by utilizing either height or weight or both The consensus is that basal metabolism is most closely correlated with the surface area DuBois and DuBois[8] have derived a formula for determination of surface area from height and weight which can be accurately applied to individuals of any size or shape regardless of bodily malformation or absence of extremities

The correlation between surface area and basal metabolism is statistical but not causal as has been most vigorously pointed out by Talbot and his associates[9] Basal heat production actually depends on the amount of active protoplasmic mass and in normal persons of average height weight and shape can be reasonably predicted by utilizing either height or weight or height and weight standards[9, 10, 11] The surface area standards are advantageous however because they can be applied to subjects of unusual shape a factor of considerable importance in endocrinological problems

Kleiber[7] in a penetrating and humorous review which deserves reading by all interested in the relation between body size and metabolic rate has concluded that the metabolic rate is more nearly proportional to surface area than to body weight He rejects however the theory that there is strict proportionality between true body surface area and metabolic rate Body surface area at best is not well enough defined Finally he recommends reference of metabolic rate to the ¾ power of the body weight as the unit of metabolic body size on the basis of recent work on animals of all sizes and shapes indicating that metabolic rate is proportional to a given power function of body weight since there exists a linear correlation between the logarithm of the metabolic rate and the logarithm of the body weight

In children and adolescents the studies of Lewis Kinsman and Iliff[13] and of Shock[14] have demonstrated that there is a smaller variation in values for normal subjects of a given sex and age if calories per square meter per hour are utilized than if height or weight figures are used The tables for predicting the basal metabolism of normal children

between the ages of 2 and 12 inclusive, offered by Lewis and his associates, are based upon studies in 52 boys and 41 girls. Shock's data are derived from studies on 50 adolescent boys and 50 adolescent girls between the ages of 11.5 and 18. The value of both these investigations lies in the fact that these small groups of children and adolescents were studied over periods of many years—longitudinal studies—in contrast to the larger series of Boothby, Berkson, and Dunn,[3] which involved single determinations in many subjects.

TABLE II

CENTRAL TREND LINE VALUES FOR CALORIES PER HOUR PER SQUARE METER OF BODY SURFACE IN RELATION TO AGE FOR BOYS AND GIRLS BETWEEN THE AGES OF 2 AND 13 YEARS INCLUSIVE

(From Lewis *et al.*, *Am. Jour. Dis. Children*, 1937, liii, 348)

Calories per Hour per Sq. M.			*Calories per Hour per Sq. M.*		
Age Years	*Boys*	*Girls*	*Age Years*	*Boys*	*Girls*
2.00	54.3	5 .6	7.75	47.7	44.7
2.25	54.0	5 .3	8.00	47.1	44.3
2.50	53.7	51.9	8. 5	46.8	44.0
2.75	53.4	51.6	8.50	46.5	43.7
3.00	53.1	51.2	8.75	46.	43.4
3.25	52.8	50.9	9.00	4 .9	43.0
3.50	52.5	50.5	9. 5	45.6	42.7
3.75	52.2	50.2	9.50	45.3	42.3
4.00	51.9	49.8	9.75	45.0	4 .0
4.25	51.6	49.5	10.00	44.7	41.6
4.50	51.3	49.	10.25	44.4	41.3
4.75	51.0	48.9	10.50	44.1	40.9
5.00	50.7	48.5	10.75	43.8	40.6
5.25	50.4	48.2	11.00	43.5	40.2
5.50	50.1	47.8	11. 5	43.	39.9
5.75	49.8	4 .5	11.50	4 .9	39.5
6.00	49.5	47.1	11.75	42.6	39.2
6.25	49.2	46.8	12.00	4 .3	38.8
6.50	48.9	46.4	12. 5	4 .0	38.5
6.75	48.6	46.1	12.50	41.7	38.1
7.00	48.3	45.7	12.75	41.4	37.8
7.25	48.0	45.4	13.00	41.1	37.4
7.50	47.7	45.0			

Our own experience extending over a period of almost two decades first with the original Aub-DuBois standards[11] and later with the modifications introduced by Boothby, Berkson, and Dunn has indicated that these standards are too high for normal children and adolescents, yielding

a high incidence of low basal metabolisms in these individuals There are not yet available entirely satisfactory standards for the younger age groups but those of Lewis Kinsman and Iliff[13] for children from through 12 years of age and of Shock[14] for children from 11 through 17 afford partly consistent and satisfactory standards for their respective age groups An inspection of the tables of Lewis *et al* and of Shock

TABLE III

Central Trend Line Values for Calories per Hour in Relation to Weight for Boys and Girls

(From Lewis *et al* *Am Jour Dis Children* 1937 LIII 348)

Weight Kg	*Calories per Hour*		*Weight Kg*	*Calories per Hour*	
	Boys	*Girls*		*Boys*	*Girls*
12.0	29.7	28.0	4 5	44.6	4 6
12.5	30.4	29.1	25.0	45.0	43.0
13.0	31.2	29.7	5 5	45.4	43.4
13.5	31.9	30.4	6.0	45.8	43.8
14.0	3	31.0	6.5	46.2	44.3
14.5	33.2	31.6	27.0	46.6	44.7
15.0	33.9	32.2	27.5	47.0	45.1
15.5	34.6	3 9	8.0	47.3	45.5
16.0	35.2	33.5	28.5	4 .6	46.0
16.5	35.8	34.1	29.0	47.9	46.4
17.0	36.5	34	9.5	48.2	46
17.5	37.1	35.4	30.0	48.5	47.0
18.0	37.7	36.0	30.5	48.8	
18.5	38.3	36.6	31.0	49.1	
19.0	38.8	37.2	31.5	49.4	
19.5	39.4	37.8	32.0	49.7	
20.0	40.0	38.4	32	49.9	
20.5	40.6	39.0	33.0	50	
21.0	41.2	39.5	33.5	50.5	
21.5	41.8	40.0	34.0	50.7	
22.0	42.3	40.4	34.5	50.9	
22.5	42.8	40.9	35.0	51.1	
23.0	43.3	4 3	35.5	51.3	
23.5	43.7	41.8	36.0	51.5	
24.0	44.1	4			

indicates considerable discrepancy at ages 12 and 13 owing to uneven increases in the latter standards at those ages For the present the safest practice is to utilize both sets of standards in those age periods where there is an overlap This is particularly important in the evaluation of hypothyroidism in hyperthyroidism the basal metabolism tends to be elevated beyond the 10 per cent introduced by shifting from one set of standards to another

TABLE IV

CENTRAL TREND LINE VALUES FOR CALORIES PER HOUR IN RELATION TO BODY SURFACE FOR BOYS AND GIRLS
(From Lewis *et al* *Am Jour Dis Children* 1937 LIII 348)

Body Surface Sq M	Calories per Hour		Body Surface Sq M	Calories per Hour	
	Boys	Girls		Boys	Girls
0.540	[illegible]9.9	28.4	0.940	44.8	43.0
0.560	30.8	[illegible]9.3	0.960	45.4	43.7
0.580	31.6	30.1	0.980	46.0	44.3
0.600	32.5	30.9	1.000	46.6	44.9
0.6[illegible]0	33.4	31.7	1.020	47.1	45.4
0.640	34.2	32.5	1.040	47.7	45.9
0.660	35.0	33[illegible]	1.060	48.2	46.4
0.680	35.8	33.9	1.080	48.8	46.9
0.[illegible]00	36.5	34.6	1.100	49.3	47.4
0.720	37.2	35.3	1.120	49.8	47.8
0.740	37.9	36.0	1.140	50.2	48.2
0.760	38.6	36.7	1.160	50.6	48.7
0.780	39.3	37.4	1.180	51.0	49.1
0.800	40.0	38.1	1.200	51.5	49.5
0.820	40.7	38.8	1.2[illegible]0	51.9	
0.840	41.4	39.5	1.[illegible]40	52.3	
0.860	4[illegible].1	40.2	1.260	52.6	
0.880	4[illegible].8	40.9	1.[illegible]80	53.0	
0.900	43.5	41.6	1.300	53.2	
0.9[illegible]0	44.2	42.3			

TABLE V

AVERAGE VALUES OF BASAL METABOLISM FOR ADOLESCENTS
(From Shock N W *Am Jour Dis Children* 194[illegible] LXIV 19)

Age Years	Calories Per Square Meter Per Hour		Age,	Calories Per Square Meter Per Hour	
	Male	Female		Male	Female
11.5	43.6	41.7	15.0	42.8	35.7
12.0	45.0	41.0	15.5	41.4	34.4
12.5	44.4	40.4	16.0	41.1	34.2
13.0	44.1	39.9	16.5	41.0	34.6
13.5	43.2	38.8	17.0	40.9	33.4
14.0	43.5	38.0	17.5	40.6	33.4
14.5	4[illegible].9	36.5			

Many standards are available for use in adults An understanding of the bases of these standards is essential in their application in the clinic

The original standards of Aub and DuBois[16] published in 1917 are satisfactory but do not segregate the yearly decrease in metabolism demonstrated by the standards of Boothby and Sandiford[31] or of Boothby Berkson and Dunn[15] The last mentioned standards are based upon large numbers of subjects tested for the first time and are therefore particularly valuable for the exclusion of hyperthyroidism The standards of Harris and Benedict[19] were based upon repeated determination upon a small number of trained subjects yielding substantially lower values than the Aub DuBois standards or their subsequent modifications

Each physician or clinic should select the standards that are most appropriate to the group of patients under study We have employed the Aub DuBois standards as modified by Boothby Berkson and Dunn[15] with satisfactory results in adults In our clinic the range of normal with these standards has been found to be between minus 10 and plus 5 per cent The standards utilized in any clinic should be checked in clear cut clinical cases of hyperthyroidism and myxedema The accurate application of standards requires observation in many patients at all levels of thyroid function as well as an adequate number of tests in each patient to establish true levels of basal metabolism All this of course implies accuracy and care in the performance of the test itself

While the determination of the basal metabolic rate is probably the simplest single test of thyroid function it should be clear that there are clinical conditions with elevation or depression of the basal metabolism which have no demonstrable relation to alterations in thyroid function The following conditions frequently are associated with persistent and marked elevations of basal metabolism (1) arterial hypertension (2) chronic heart disease with or without myocardial failure (3) malignant lymphoma and chronic leukemia (4) polycythemia vera (5) pheochromocytoma (6) acromegaly Abnormally depressed rates of basal metabolism are regularly encountered in undernutrition anorexia nervosa Addison s disease and non thyrogenous hypometabolism In panhypopituitarism (Simmonds disease) the basal metabolism is always low but here there is failure of thyroid function secondary to the pituitary disease with failure of thyrotrophin production The differential diagnosis between these conditions and thyroid disease depends therefore on diagnostic procedures other than basal metabolism determination

Protein bound (Precipitable) Iodine of the Blood in the Diagnosis of Thyroid Disease

In the preceding Part the physiological significance of the protein

bound iodine of the blood was discussed, the essence of the matter being that the protein bound iodine is a measure of circulating thyroid hormone reflecting therefore the state of thyroid function. This has been more conclusively demonstrated by Taurog and Chaikoff[17] who employed radioactive iodine to study the nature of the iodine contained in plasma. First they demonstrated that 90 per cent of the plasma iodine behaved like thyroxine in its solubility properties, secondly by utilizing thyroxine as a carrier for radio iodine extracted from plasma they showed through repeated recrystallization that this radio iodine containing material was in the same chemical form as thyroxine and thirdly by employing immiscible solvents they found that the distribution of radio-iodine and ordinary iodine in plasma was the same.

The measurement of protein bound iodine affords therefore an accurate index of circulating hormone, and since circulating hormone reflects the functional activity of the thyroid its estimation has a definitive value. The amounts of iodine dealt with are small ranging from 0.5 to 35 micrograms per 100 cc. of blood and require exacting and arduous methods. With current methods the range of normal varies from 3.5 to 8 gamma per 100 cc. of blood[18, 19, 20, 21, 22, 23]. The serum protein-bound iodine is markedly depressed or absent in myxedema and cretinism and elevated in hyperthyroidism. In normal pregnancy values between 6.2 and 11.2 gamma per 100 cc. of serum have been reported[7]. This elevation occurs by the end of the first month.

The determination of the protein-bound iodine combined with basal metabolism levels and the uptake of radioactive iodine represents in our opinion the most precise laboratory tests available for the evaluation of function in thyroid disease. The measurement of the blood protein bound iodine has many advantages. The blood sample can be drawn at any time, does not require the fasting state or patient co-operation as in the basal metabolism test. The serum can be frozen and tested at any time or can be sent to laboratories capable of performing the test accurately. It is particularly advantageous in patients in whom it is impossible to obtain an accurate or a true basal metabolic rate. In congestive heart failure associated with either thyrotoxicosis or myxedema the basal metabolism will reflect a higher level of thyroid function than actually exists, the precipitable blood iodine level will be diagnostically helpful. In mentally disturbed or psychotic patients the determination of the blood iodine level may be the only laboratory test that can be utilized. Similarly in infants and children it is especially valuable requiring minimal co-operation.

The defects or disadvantages in the use of the blood protein bound iodine for diagnosis hinge upon the chemical fact that inorganic iodides administered for therapy or organic iodine containing compounds used for diagnostic roentgenography will cause an elevation in the protein bound iodine of considerable degree and for a relatively long period. Danowski and his co workers [4, 5] have shown that the administration of large amounts of inorganic iodides (up to 7 gm daily) is associated with increased levels of the protein bound iodine. The maximal levels ranged from 1 to 3 micrograms per 100 cc of serum and the elevated levels required many weeks to return to normal. These rises in protein bound iodine, as has already been pointed out (Part II), occurred in the non thyroxine fraction and were without metabolic effect. The administration of inorganic iodide in a daily dose of 0.2 to 0.6 gm over periods up to 50 days will frequently cause elevations in the protein bound iodine to high normal or slightly hyperthyroid levels. These levels will return to normal in one to two weeks after the omission of iodide.

Radio opaque dyes containing organically bound iodine will elevate the protein bound iodine level for prolonged periods depending upon the dye utilized. Since iodopyracet (Diodrast) is eliminated rapidly if kidney function is normal, reliable values for protein bound iodine may be obtained after two weeks. Iodoalphionic acid (Priodax) is more slowly excreted and reliable values for the protein bound iodine may not be obtained for at least 1 weeks. Iodized oil (Lipiodol) is most troublesome since it is excreted slowly and irregularly; deposits of the dye may linger in the subarachnoid space and elevate the protein bound iodine for so many months that the test is rendered impractical in patients who have received this dye.[6]

Mercurial diuretics may lower the protein bound iodine of the blood for at least 24 to 48 hours depending upon the rate of excretion of the mercury. This results in false low values owing to the formation of insoluble mercuric compounds that prevent distillation of the iodine in the course of chemical analysis.[7]

Use of Tracer Doses of Radioactive Iodine in the Diagnosis of Thyroid Disease

The employment of tracer doses of radioactive iodine in the study of thyroid physiology has been discussed fully in Part II. This technique yields information that is useful in the diagnosis of thyroid hyperfunction in patients with diffuse and nodular goiters and, to some extent, in hypo

thyroidism and certain types of thyroid malignancy, such as the highly differentiated malignant adenomas and the so called benign metastasizing goiters While radioactive iodine has been made readily available at little or no cost by the United States Government, the utilization of this substance in the diagnosis of thyroid disease is necessarily limited by the need for proper facilities and special equipment required by the method The need for protection of personnel from radioactivity imposes still further restrictions on its use

Tracer studies with radio iodine may be carried out by measurements with a single- or multitube Geiger counter placed externally over the thyroid gland or by quantitation of the urinary excretion of administered radio-iodine over a 2- or 3-day period Single-tube Geiger counters are no less accurate than the multitube counters [9] Astwood and Stanley [1] have utilized external counts over the thyroid both as an aid in the diagnosis of hyperthyroidism and as a convenient and accurate method of assaying the antithyroid action of goitrogens in humans Normal subjects gradually accumulate radio-iodine after a standard tracer dose over a period of hours reaching counts of 10 to 35 per second In thyrotoxicosis the gland rapidly takes up radio iodine reaching counts in two hours of 60 to 240 per second All of the 41 thyrotoxic patients studied had distinctly greater collections than the largest collections in normal subjects

Freedberg and his associates [30] studied thyroid function in euthyroid hyperthyroid and hypothyroid patients by means of a 4 tube method In euthyroid subjects the average 24 hour thyroid gland uptake has measured about 35 per cent with a range of 16 to 45 per cent As may be seen in Fig 40 some euthyroid patients with complicating factors will take up as much as 65 per cent and very rarely slightly more Entirely normal subjects free of goiter, congestive heart failure or any type of thyroid disease in their past history shows an average uptake that is even lower namely 29 per cent with a range of 16 to 40 per cent and rarely up to 45 per cent Euthyroid patients who have had thyroidectomy for hyperthyroidism show normal uptakes Euthyroid patients with nodular or diffuse goiter congestive heart failure and previous therapy for thyrotoxicosis with I^{131} exhibit somewhat higher values of uptake averaging 39 per cent or 10 per cent above strictly normal controls This group accounts for all the abnormally high uptakes in euthyroid patients (Fig 40)

In thyrotoxicosis the average 24 hour uptake of radio iodine is about 71 per cent When thyrotoxicosis is associated with nodular rather than

with diffuse enlargement of the thyroid gland however the average uptake is about 60 per cent In patients persistently hyperthyroid after radio iodine therapy the average uptake does not differ from that of untreated patients with toxic diffuse goiter The range of uptake in hyperthyroidism may be from 41 to 95 per cent thus overlapping in the

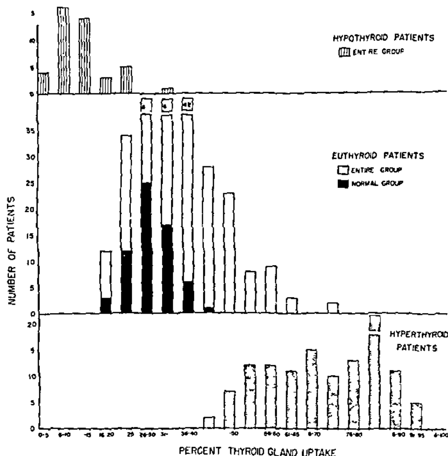


Fig 40 I131 tracer uptakes in euthyroid hyperthyroid and hypothyroid patients Reproduced from Freedberg A S Chamovitz D L and Kurland G S Metabolism, 1952 1 32

lower range that of euthyroid individuals It should be noted however that with sensitive and accurate measurement of radio iodine uptake or excretion 94 to 98 per cent of thyrotoxic patients will have uptakes over 50 per cent or excretions below 50 per cent [3, 31, 3]

In myxedema there is an average uptake of 12 per cent with a range of 0 to 25 per cent Here again, there is overlap between the hypothyroid and euthyroid patients

The various factors influencing the uptake of radio iodine by the thyroid must be noted for proper interpretation of its measurement The cause of the increased uptake in non-toxic nodular goiter is unclear since most nodules have a lower uptake of radio iodine than the perinodular thyroid tissue In congestive heart failure there is a somewhat increased uptake of radio iodine and in severe renal disease there is a decreased excretion of the isotope In both conditions impaired kidney function may be the responsible factor allowing prolonged recirculation of radio iodine and therefore an opportunity for increased pick up by the thyroid gland

Repeated administration of tracer doses of 100 to 150 microcuries of carrier-free I^{131} has no influence on uptake or turnover Ingestion of stable iodide in amounts greater than 100 micrograms will partly or completely block I^{131} uptake for as long as 3 weeks in thyrotoxic patients and 10 weeks in euthyroid subjects Stable iodide administered 3 or more days after a therapeutic dose of I^{131} in thyrotoxic and euthyroid patients without edema or congestive heart failure produces only a slight increase in urinary I^{131} with no appreciable decrease in thyroid radioactivity[31] However the administration of stable iodide to thyrotoxic patients 24 to 48 hours after a therapeutic dose of I^{131} results in considerable loss of I^{131} from the thyroid gland[30]

Organic iodine containing compounds employed in roentgenography will also block uptake of I^{131} by the thyroid gland Iodoalphionic acid (Priodax) is excreted slowly and will block uptake for as long as 8 months, whereas iodopyracet (Diodrast) will have a more transient blocking effect lasting no more than 5 days

Desiccated thyroid in therapeutic doses will depress uptake of I^{131} for many weeks In one patient uptake remained blocked for 34 weeks following thyroid administration[30, 31, 3] Potassium thiocyanate administered in doses of 2 gm one to one and a half hours either before or after a tracer dose of I^{131} caused considerable depression of uptake which persisted for at least one week[30] The administration of propylthiouracil will cause an increased uptake of I^{131} in thyrotoxic and euthyroid patients following the omission of the drug This increased uptake reaches a maximum 5 to 7 days after the propylthiouracil is stopped During the administration of propylthiouracil however, uptake of I^{131} is markedly depressed[30, 31, 3]

Corticotrophin (ACTH) significantly depresses radio iodine uptake by the thyroid gland with quick recovery to normal within days after omission of the hormone The effect of cortisone on I^{131} uptake is not *uniform* [31, 33, 34] *

The studies of Freedberg and his associates [31] confirm for the most part the earlier studies of Keating and his co workers [3] The latter investigators compared four methods of measuring radio iodine accumulation including (1) the measurement of the quantity of radio iodine excreted in the urine within 48 hours after its administration (2) determination of the extrarenal disposal rate from analysis of the curve of urinary radio iodine excretion (3) in vivo measurement of the quantity of radio iodine accumulated in the thyroid gland 4 hours after administration of the dose and (4) determination of an in vivo accumulation rate They found that all four methods had similar diagnostic sensitivity but that method 3 provided more accurate information in the presence of reduced or absent iodine accumulation than did method 1 whereas method proved superior in providing the clearest picture of the state of radio iodine function particularly in situations complicated by altered renal function

Myant Pochin and Goldie [3] have found the thyroid clearance rate a most sensitive and direct index of thyroid function since in all thyrotoxic patients studied it considerably exceeded the highest value observed in normal subjects They calculated the clearance as the ratio between rate of rise of thyroid content of I^{131} and the corresponding plasma concentration of radio iodine The thyroid clearance rate was thus derived from three factors each of which is altered in thyrotoxicosis (1) the average maximum count over the thyrotoxic gland was found to be three times that in controls (2) the time by which half this value was reached averaged 0 9 hours in thyrotoxicosis as against 4 5 hours in controls and (3) the plasma concentration in control subjects was

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* Berson and Yalow however have evaluated the effect of cortisone on thyroid function by studies of thyroidal and renal plasma I^{131} clearance rates and for 24 hour thyroidal uptake and renal excretion measurements in 4 euthyroid subjects They found that doses of 100 mg a day or more regularly produced with but a single exception marked inhibition of the iodine accumulating function of the thyroid gland and usually produced an elevation of the renal plasma I^{131} clearance rate In almost all cases return to pre treatment levels occurred within days to a week following omission of the drug or reduction of dosage to 50 mg a day or less Under continued therapy the thyroid inhibition became progressively more marked but renal clearances tended to return toward pre treatment level in some cases (Berson S A and Yalow R S Effect of cortisone on the iodine accumulating function of the thyroid gland in euthyroid subjects, Jour Clin Endocrinol and Metabol 195 xii 407)

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Geiger Muller counter has been used to study the spatial distribution of radio iodine in the human thyroid gland[37] In the normal thyroid I^{131} is concentrated uniformly throughout the gland with the greatest con centration recorded over the middle of each lateral lobe where there is a maximum depth of tissue The directional counter is especially useful in demonstrating the presence of functioning thyroid tissue in an abnormal site or the absence of function in what is apparently thyroid tissue Thus hot nodules or hyperfunctioning nodules of the thyroid can be readily picked up by the directional counter which will show maximal iodine uptake over the site of the nodule The cold nodules or non functioning nodules will show no activity over the site of the nodule or nodules

The directional scintillation counter has proved useful in the estimation of gland size and weight and therefore in more precise determination of therapeutic doses of radio iodine[38, 39] This instrument is used to deter- mine the count rate for a series of co ordinate points over and around the area occupied by the thyroid gland By drawing a line through the series of isocount points representing the margin of the lobes of the thyroid an outline of the gland is obtained This procedure has been greatly facilitated by the development of an automatic scanning device and a visual recorder which produce a scintigram of the thyroid gland in from 15 to 30 minutes[41] This instrument permits visual follow up of I^{131} therapy in patients with hyperthyroidism and has shown progressive decrease in size of the goiter starting in the second week following therapy with doses ranging from 2 to 12 millicuries[40] It has also proved valuable in differentiating nodules that accumulate I^{131} from those that do not and in the follow up of thyroid cancer patients where it will disclose functioning metastatic nodes before they become palpable

Quantitative measurement of the urinary excretion of radio iodine gives indirect information of its uptake by the thyroid gland Our experience with this method has been limited to patients with diffuse and nodular goiters showing either normal or increased thyroid function and has been in accord with that reported by Skanse[31] and Keating and his co workers[3] It is a less specific measure of thyroid function than measurement of thyroid gland uptake and may give inexact and mis- leading information

As a diagnostic procedure tracer studies have not proved as conclusive as the determination of the protein bound iodine in the blood This is due for the most part to the significant overlap among the several categories of thyroid function We agree with the following statement

about 2.5 times that in thyrotoxic patients at 1 hour after the dose. These investigators feel that the thyroid clearance rate measures directly the activity of the thyroid in taking up iodine from the plasma. If both the rate at which radio-iodine is entering the thyroid and the simultaneous plasma concentration of radio-iodine are known, then the volume of plasma cleared of radio-iodine in unit time can be calculated. In normal subjects about 16 milliliter of plasma are cleared of iodide per minute by the thyroid. In 11 untreated thyrotoxic patients the clearance rate averaged 486 milliliter per minute, with values ranging between 200 to 1400 milliliter per minute in individual patients. The renal clearance rate for plasma radio-iodine averaged about 30 milliliter per minute both in normal and in thyrotoxic subjects.

Berson and his associates [11] have also utilized determinations of thyroidal and renal plasma I^{131} clearance rates as a routine diagnostic test of thyroid dysfunction. These investigators employed a simple method of obtaining the thyroidal and renal plasma iodide clearances without the necessity of performing analyses of blood samples. The method is based on an observed relationship of relative constancy between the body weight and the space of I^{131} dilution during the first half hour following intravenous administration of the isotope. The clearance rates were readily determined in a single 35-minute sitting from the assay of radio-activity in the neck and in a single urine specimen. The clearance rates and the 24 hour thyroid uptake and renal excretion values for 87 euthyroid, 18 untreated hyperthyroid, 5 treated hyperthyroid and 5 hypothyroid patients were quite in accord with those obtained by the Mayo Clinic group [3] and by Myant and his associates [35] with their more elaborate methods. The lowest thyroidal clearance rate in hyperthyroidism was almost twice the highest rate in euthyroidism. Nevertheless overlaps between euthyroid and hyperthyroid 24 hour values occurred in about 7 per cent of normal subjects who showed clearance rates in the hyperthyroid range.*

The application of newer and more precise tools has greatly aided the diagnosis of thyroid function by means of radio-iodine. The directional

* Kriss has studied thyroid uptake of radio-iodine after intravenous administration of 40 to 100 microcuries of carrier free I^{131} in euthyroid subjects and in patients with various thyroid disorders. The uptake one hour after administration of the tracer dose exhibited excellent correlation with the degree of clinical thyrotoxicosis. This method appeared more advantageous than the 24 hour oral method in that it was more rapid and accurate, reducing the overlap in values between euthyroid and hyperthyroid patients. (Kriss, J. P.: Uptake of I^{131} after intravenous tracer doses. Jour. Clin. Endocrinol. 1951, xi, 289.)

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As a diagnostic procedure tracer studies have not proved as conclusive as the determination of the protein bound iodine in the blood This is due for the most part to the significant overlap among the several categories of thyroid function We agree with the following statement

of Keating and his associates.[39] "Measurement of radioiodine accumulation is considered to be comparable but not superior to determination of basal metabolic rate as a measure of thyroid function. It appears likely that it will supplement rather than supplant other diagnostic aids."

Blood Cholesterol in the Diagnosis of Thyroid Disorders

The role of the thyroid in fat metabolism has been discussed in Part I. Diagnostic alterations in all of the lipid constituents of the blood except the neutral fat content may occur in both hyperthyroidism and hypothyroidism. These alterations occur primarily in the serum with slight changes in the lipid values of the cells. Hyperthyroidism tends to lower the blood cholesterol and hypothyroidism more consistently elevates the blood cholesterol. Because of the wide range of normal values, significant shifts in the blood lipid values may not be appreciated until the establishment of euthyroidism returns the lipid content to values normal for the individual. Patients with normally high or normally low cholesterol content of the blood will show more striking elevations in myxedema or depressed values in thyrotoxicosis than patients with average normal values.[41] The wide range of normal values from 150 to 250 mg. per 100 cc. may obscure significant changes due to thyroid disease except as they change with amelioration of abnormal thyroid function. Other diseases that alter the blood cholesterol may co-exist with thyrotoxicosis and obscure the blood changes; this is especially true in diabetes and nephritis.

Measurement of the Circulation Time in Thyroid Disease

The velocity of blood flow is significantly increased in thyrotoxicosis and decreased in myxedema so that its measurement affords diagnostic information about the state of thyroid function in the absence of other influencing conditions such as anemia, heart failure, polycythemia and fever. The speed of circulation time at different levels of thyroid function is a reflection of the metabolic demands of the body, increasing with thyrotoxicosis and slowing with myxedema.[4, 43] Calcium gluconate[44] and sodium dehydrocholate[4] have been found useful for the clinical determination of the circulation time. With these substances arm to tongue circulation time in the normal averages 12.5 to 15 seconds. In thyrotoxicosis it may be as rapid as 7 seconds but averages about 8.5 seconds. In myxedema it is usually prolonged to between [illegible]5 and 30 seconds.

Electrocardiogram in the Diagnosis of Thyroid Function

The preceding tests have demonstrated changes that were relatively specific in measuring the level of thyroid function Electrocardiography however is of diagnostic value only in hypothyroidism and in this condition it is likewise useful as an indicator of the response to thyroid medication Specific changes have been shown to occur in leads 1 2 3 and CF4 no adequate study has yet been reported of changes in unipolar limb or precordial leads In myxedema the electrocardiogram shows a strikingly low voltage in all complexes slight prolongation of the P R interval and lowering flattening or inversion of the T wave[46 47 48] Q wave changes such as occur in myocardial infarction have not been reported These changes are completely reversible following the administration of thyroid medication In thyrotoxicosis the electrocardiogram may show tachycardia or auricular fibrillation but no changes specifically diagnostic of increased thyroid function

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PART VI

NON-TOXIC GOITER

I NON TOXIC DIFFUSE GOITER

II NON TOXIC NODULAR GOITER

III INTRATHORACIC GOITER

I NON TOXIC DIFFUSE GOITER

Introduction

Definition A diffuse and symmetrical enlargement of the thyroid generally *associated with normal thyroid function occurring in either* sporadic or endemic form

Synonyms Simple goiter endemic goiter colloid goiter adolescent goiter iodine deficiency goiter

Historical *This disease has been recognized and described for over 2 000 years It is mentioned in the writings of Celsus Pliny Vitruvius* Juvenal Aetius of Amida *Roger of Palermo Marco Polo and Paracelsus* A comprehensive account of the thyroid gland in medical history has been *published* by Jason[1]

Distribution and Incidence

Geographic distribution is the most striking aspect of this thyroid disorder It is found endemically in old glacial areas and in the great mountainous regions of the world where practically the entire population—animal as well as human—is affected In such districts the incidence of goiter is frequently inversely proportional to the iodine content of the water soil and air It appears at birth or in early childhood in endemic areas and at puberty or during adolescence in non endemic regions There is little or no sex difference in endemic areas but in non

goiter regions the sex ratio is 7 or 8 to 1 in favor of the female The peak of incidence is earlier by two or three years in boys than in girls, in both goitrous and non goitrous districts

The geographical incidence is of considerable interest because it has given rise to several theories concerning the pathogenesis of this type of goiter In North America the goitrous areas as revealed by thyroid surveys, comprise the Great Lakes region especially Michigan and Wisconsin the states of the northern Pacific coast, and the upper valley of the Mississippi River The North Atlantic states Maryland the South Atlantic states and those extending along the Gulf of Mexico through Texas and New Mexico have a minimal incidence of goiter In South America goiter is prevalent in the Andes and the Cordilleras In Europe the highest incidence is found in the Alps and the Pyrenees In England the highest incidence is in the Thames Valley and Derbyshire In Asia the Himalayas Caucasus Ural Altai and Japanese mountains contain areas of high goitrous incidence The oases of the Sahara the Sierra Leone, Egypt parts of the Congo and the Abyssinian Mountains represent the goitrous regions of Africa New Zealand Madagascar Ceylon Borneo Sumatra and Java all have areas of endemic goiter

Although endemic goiter is found in the mountains in the deserts and along the sea coast the percentage of the population affected in such regions as the Swiss Alps and the Himalayas is far higher than in any part of the United States or Great Britain McCarrison found a 100 per cent incidence in parts of the Gilgit district of India and Wegelin[3] could find no normal thyroid gland in autopsies in Berne Switzerland All surveys and all investigators have found great paradoxes in the geographical incidence Valleys in close proximity, served by the same watershed may have a striking difference in goiter incidence Even non goitrous Massachusetts has been found to have areas of endemic goiter in Berkshire County[4]

Etiology

Chatin[5,6,7] in a series of investigations beginning in 1850 carried out extensive analyses of the iodine content of air water soil plants and animals and concluded that iodine deficiency was the principal cause of goiter and cretinism On the basis of these findings he suggested that endemic goiter could be prevented by iodination of the water supply A commission of the French Academy after an investigation of Chatin s reports found itself unable to accept his conclusions about etiology and

recommendations for prophylaxis Since then numerous investigators particularly McClendon[8] in the United States Von Fellenberg[9, 10] in Switzerland and Hercus[11, 12, 13] in New Zealand have attempted to show that endemic goiter is caused in the first instance by an absolute deficiency in iodine content of the environment—air water soil and food The evidence for this point of view depends upon a correlation of iodine analyses involving parts of iodine per hundred billion parts of water with the incidence of goiter as found by physical examination of army recruits school children and in some instances more wide spread sampling of the population The difficulties in this type of study are apparent On the one hand there is considerable evidence of the inaccuracies of the methods used for iodine analysis and on the other hand a uniform clinical evaluation of goiter incidence is not simple Aside from these difficulties there are important exceptions to the alleged relation of goiter incidence to exogenous iodine deficiency These exceptions in turn in many instances also depend upon inaccurate iodine analyses or inadequate clinical evaluation of goiter incidence

Ucko[14] and Greenwald[15] have again called attention to the weak support lent to the iodine lack theory of goiter causation by water soil and food analyses Ucko points out that this theory is concerned with two distinct problems (1) Is an inadequate supply of iodine to the thyroid gland the immediate cause of goiter (2) If so are goitrous districts insufficiently iodinized and is this the cause of a deficient iodine supply to the thyroid gland Regarding the first question most investigators agree that lack of iodine plays a significant part in the pathogenesis of goiter but the role of other causative agents requires further study The occurrence of sporadic as well as endemic goiter and the difference in the morphology of goiters from mountainous and non mountainous regions suggest that there may be more than one causative factor The recent knowledge of goitrogenesis obtained from the study of goitrogenic agents in plants and thiourea derivatives (see Part iii) certainly is in accord with such a probability Some of these agents clearly owe their goitrogenic effect to interference with the utilization of iodine by the thyroid gland and thus produce a conditioned iodine deficiency However animal experiments with iodine poor diets with attempts to prevent this dietary goiter by addition of small doses of iodine have not given conclusive results Moreover goiter can be produced experimentally by a variety of factors such as exposure to cold high protein or fat diet starvation and excess of calcium intake Hellwig[16, 17] and Thompson[18] have demonstrated that iodine poor diets pro

duce goiter more readily when they contain an excess of calcium and that iodine deficiency alone is followed often by atrophy of the gland McClendon and Foster[10] in a carefully controlled experiment, have produced goiter in a small number of rats fed iodine free diets derived from nutrients grown by hydroponics and concluded that goiter can be produced solely by iodine-lack

Critical study of the available evidence makes clear that multiple factors are involved in the causation of endemic and sporadic goiter Purely exogenous or a conditioned endogenous iodine deficiency may prove to be the ultimate cause but the definitive etiology is still unsettled

The existence of iodine deficiency in goitrous regions and its relation to goitrogenesis is likewise not well substantiated, according to Ucko[11] The methods used for iodine analysis of food, soil and water proved unreliable and yielded answers that were not reproducible in the hands of experienced chemists The estimation of goiter incidence was similarly inaccurate The criteria used were variable and observers frequently disagreed by large percentages about the incidence in the same locality Furthermore endemic goiter has occurred in iodine rich areas with endemic foci near the sea and a high iodinization of the environment Moreover there is lacking an adequately inverse relation between goiter incidence and iodinization in many areas

McCarrison[9] Blacklock[1] and Chagas have claimed that goiter is of infectious origin but this point of view has gained few adherents McCarrison, himself has stressed a low iodine intake as essential for the production of goiter through either water pollution or other noxious agents

PATHOLOGY

In Part iv, the relation of thyroid morphology to iodine metabolism has been extensively discussed In non-toxic diffuse goiter the essential pathology varies considerably but the changes involved are closely analogous to those observed in the experimental animal following the administration of thyrotrophin iodine deprivation or treatment with the antithyroidal goitrogens The pathological changes follow the Marine cycle of hyperplasia involution with atrophy as a final stage in cases where the demand for hormone is unduly intense and prolonged without adequate iodine availability Regardless of the over all picture of any thyroid gland detailed examination will usually disclose areas of pathology ranging from hyperplasia to involution

In endemic or sporadic goiter the gland is soft and diffusely enlarged The cut surface appears pale pink and slightly translucent because of its colloid content The connective tissue stroma is considerably increased giving rise frequently to pseudo lobulation The histologic appearance will vary according to the age of the goiter its stage of involution, and the geographical region of its origin and evolution Typically the acini vary greatly in size are lined with a flat epithelium and are filled with dense colloid Blood vessels are scarce or compressed by the overfilled acini Scattered areas of hyperplasia may be observed Early lobulation surrounded by thickened stroma may also be observed The geographical pathology is important because the histology of goiters arising in areas of high endemicity such as Switzerland and the Himalayas as well as that of congenital goiters in these regions differs strikingly from the histology of colloid goiters of North America or England The typical histology in the former areas consists of goiter due to increased epitheleal hyperplasia without important colloid deposits The gland is firm large and somewhat vascular with a pale fleshy appearance The acini are greatly increased containing little or no colloid the cells tend to be columnar and there may be papillary infoldings as in thyrotoxicosis It is therefore called a parenchymatous goiter With age it becomes converted into the usual colloid or nodular goiter rarely appearing after puberty This type of goiter is frequently associated with subnormal thyroid function or cretinism despite the histological picture of intense hyperplasia

Symptoms and Signs

This form of goiter is generally asymptomatic In non goitrous regions, its presence may be unnoticed by the patient until observed by others or by the physician In endemic areas the goiter is usually larger and the patient is more frequently aware of its existence The production of symptoms depends upon the size consistency rate of growth and degree of intrathoracic extension Very large goiters may produce exertional dyspnoea through compression of the trachea especially the more readily compressible trachea of children and young adults Rapid growth may similarly produce dyspnoea Spasmodic non productive cough stridor hoarseness and dysphagia are seen only with intrathoracic extension Rarely bradycardia and syncope may result from pressure of the goiter upon the carotid sinus

On examination, the thyroid is found to be diffusely enlarged in varying degree with ill defined borders The consistence of the goiter likewise varies from soft to firm and tense but never hard with a smooth surface except in the case of large long-standing goiters where a lobulated surface may be felt Thrills and murmurs over the surface of these glands are rarely encountered Intrathoracic extension may produce distention of the neck veins but this degree of extension very rarely occurs in this type of goiter

In the vast majority of cases thyroid function remains normal but occasionally failure of adequate hormone production may occur In such instances the clinical and laboratory findings of hypothyroidism will be present

Clinical Course

In endemic regions the goiter first appears in early childhood more frequently in girls than in boys whereas in non goitrous districts it is not seen until puberty and is again much more common in girls In these latter districts diffuse thyroid enlargement may appear only during pregnancy in a considerable number of cases Once the goiter has developed it may slowly regress and disappear or it may remain unaltered Increase in size and the development of nodules usually occurs in the third or fourth decade of life This is particularly true of long standing goiters The nodules in turn may remain stationary or increase in size but they rarely regress The development of hyperthyroidism in this type of goiter is exceedingly rare Pregnancy may increase the size of an existent goiter with incomplete recession after parturition

Diagnosis

The diagnosis depends upon the finding of a diffuse soft symmetrical enlargement of the thyroid without associated clinical or laboratory signs of hyperthyroidism When this type of goiter occurs in individuals with neurocirculatory asthenia or with rheumatic heart disease there may be a simulation of thyrotoxicosis In the first instance there may be present an elevation of the systolic blood pressure tachycardia tremor and sweating with a history of nervousness and palpitation In the second instance there may be a history of palpitation and dyspnoea in association with a hyperactive heart In these instances the diagnosis can

be made secure by repeated observation of the basal metabolism Measurement of the protein bound iodine in the serum is particularly conclusive If this facility is lacking a diagnostic test with iodide medication for a period of 10 to 14 days will usually be helpful

Measurement of the uptake of radioactive iodine is not diagnostic as uptakes in the thyrotoxic range may occur because of the iodine avidity of these goiters Stanbury and his associates [3] have found extremely high uptakes in the endemic goiter of the Andes region of Argentina These patients were all euthyroid Large colloid goiters in non endemic areas often demonstrate an uptake of radioactive iodine well beyond the average normal of euthyroidism though not so high as in the areas of goiter endemicity

In patients with large asymptomatic goiters regardless of size and especially in patients with cough or hoarseness roentgenography of the chest in both antero posterior and oblique views as well as laryngeal examination is essential for the demonstration or tracheal deviation and compression or recurrent laryngeal nerve injury

Prophylaxis and Treatment

Non toxic diffuse goiter is more readily prevented than cured This simple type of goiter is by itself not serious but its sequelae in the form of endemic cretinism thyrotoxicosis and thyroid malignancy have given rise to public health problems of world wide scope Regardless of the ultimate cause of endemic and sporadic goiter there is agreement that the thyroid gland will maintain a normal structure and function if an adequate supply of iodine is available to it The brilliant results of the prophylaxis of endemic goiter in man through the supply of adequate amounts of exogenous iodine date back to the work of Marine and Kimball in 1917 [4] These workers after a trial of several methods of supplying adequate environmental iodine concluded that iodized table salt offered an inexpensive effective and practical means of achieving satisfactory prevention of endemic goiter In a recent re evaluation of the subject by Kimball he concludes that the persistent use of iodized table salt will cause highly significant reductions in the incidence of goiters in school children For instance a survey of over 61 000 children in Grand Rapids Michigan showed a decrease of goiter from 38 6 per cent in 19 4 to 8 2 per cent in 1936 In other communities in Michigan and Ohio the use of iodized salt has been regularly followed by similar decreases in the incidence of goiter

Wegelin [c] describes the results of the campaign against goiter in Switzerland Prophylaxis by the use of iodized table salt was begun in the years 1922 to 1924 The use of this salt was gradually made obligatory in an increasing number of Swiss cantons Examination of the thyroid gland at birth for goiter, a sensitive index of the efficacy of iodine

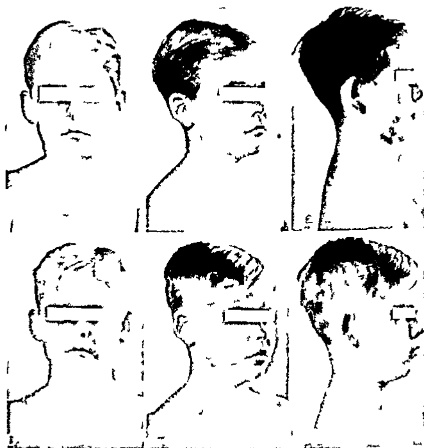


Fig 41 Case 4 J L E a boy 11 years of age with diffuse non toxic goiter A shows the goiter before oral administration of thyroid B semiprofile view C, profile view D after eight weeks of treatment with 3 grains (0 120 gm) thyroid per day note disappearance of the goiter E, semiprofile view F profile view From Rienhoff W F, Jr Arch Surg 1940 xli 487

prophylaxis has shown an increasingly higher proportion of normal glands Cogenital goiter has largely disappeared and even the percentage of glands showing minimal enlargement has decreased from 70 per cent to 7 per cent

The amount of potassium iodide used in table salt has varied from 1 part per 100 000 to 1 part per 200 000 Too large quantities of iodide do indeed increase the likelihood of iodism but there is now substantial evidence that Jod Basedowism—i e induction of thyrotoxicosis in nodular goiter by iodides—is essentially nonexistent

The treatment of diffuse non toxic goiter is best accomplished by the use of desiccated thyroid (U S P) in daily dosage of 60 to 180 mg Physiologically the administration of thyroid hormone will reduce thyrotrophin secretion—an all important factor in the production and maintenance of hyperplasia of the thyroid the invariable early stage of colloid goiter In addition it supplies the body with adequate thyroid hormone exogenously allaying the demands of the organism upon its own thyroid Rienhoff [7] has demonstrated the effect of thyroid extract in the production of atrophy of the thyroid gland in man through serial biopsies Rapid regression of the goiter over a period of weeks or months has occurred in many instances We ourselves have regularly observed this effect in diffuse goiters The use of iodides has proved valuable in occasional cases only though they can be used without fear of the production of hyperthyroidism Iodides may best be utilized in the form of potassium iodide in saturated solution or as compound solution of iodine (Lugol s solution) in daily doses of 5 drops (Fig 41)

Treatment with either thyroid extract or iodides should be continued for months and even years after the goiter has regressed in order to prevent recurrence

Subtotal thyroidectomy is indicated when pressure symptoms and signs are present or for cosmetic reasons when the goiter is large and disfiguring

II NON TOXIC NODULAR GOITER

Introduction

Definition An irregular enlargement of the thyroid gland containing one or more discrete nodules and usually associated with euthyroid function

Synonyms Adenomatous goiter *struma nodosa adenomatosis of the thyroid*

Distribution and Incidence

Nodular goiter occurs with greatest frequency in areas of high endemicity in somewhat later age groups than those in which diffuse goiter appears being particularly common after the age of 30 This later age incidence is due to the fact that most nodular goiters evolve from preexistent diffuse colloid goiters The relative frequency at autopsy of nodular goiter in endemic and non endemic districts has been quite extensively reported in Europe [28, 30] but has received inadequate attention in America Rice [31] studied the incidence of thyroid nodules in Minnesota, a goitrous region while Schlesinger, Gargill and Saxe [3] reported on the incidence in routine autopsies in three teaching hospitals in Boston Massachusetts, a non goitrous region Rice s series was smaller than that of the latter authors comprising only 390 autopsied cases as contrasted with 1373 from the Boston hospitals Both series were based on the incidence of macroscopic nodules In Minnesota, nodules occurred in about 57 per cent of autopsies whereas in Boston the average incidence was found to be about 8 per cent In both districts there was increasing incidence with advancing age so that in the goitrous area in persons between 70 and 75 years of age 100 per cent of the thyroids contained nodules In Boston nodules were twice as common in women and in those over the age of 50 the incidence approached 40 per cent

Etiology

Nodular goiter is generally regarded as a result of long continued goitrogenic influences particularly iodine deficiency This form of goiter is abundant in endemic regions especially in persons who have previously had diffuse non-toxic goiter Its incidence is markedly reduced by goiter prophylaxis Nevertheless, this is not the whole story for adenomatous goiter is frequently seen in individuals who have never resided in goitrous areas and who have never had a colloid goiter A small number of nodular goiters will represent various types of benign or malignant neoplasms The etiology of this latter group is not necessarily related to the problem of the genesis of the usual nodular goiter

The production of nodular goiter in the experimental animal was first reported by Wegelin [33] and Hellwig [34] who noted the development of thyroid adenomata and occasionally metastasizing thyroid carcinoma and sarcoma in rats kept on diets that produced a persistent hyperplasia of the thyroid Griesbach and his associates [3] found that prolonged

and continuous thyroid hyperplasia produced by the goitrogens in Brassica seeds led to the formation of thyroid nodules in the rat whereas intermittent cycles of hyperplasia and involution did not lead to colloid or nodular goiter in that animal thus affording no support to the hypothesis of Marine[34] Griesbach concluded that nodular goiter was due to long continued stimulation of the thyroid by thyrotrophin The pituitary glands of these rats all showed varying degrees of overactivity particularly evidenced by changes in the basophil cells these cells had previously been demonstrated by these workers to be responsible for thyrotrophin production Kuzell and his associates[37] have also found a high incidence of nodular hyperplasia of the thyroid in rats maintained for prolonged periods on high intakes of thiouracil

Pathology

The macroscopic appearance of nodular goiter varies greatly The nodules may be single or multiple tending to be solitary in areas of sporadic goiter and multiple in endemic regions The degree of capsule formation the amount of connective tissue and the presence of calcification will depend upon the duration of the goiter Capsulation is well marked with larger or long standing nodules but poorly encapsulated multiple nodules of small size may give rise to very large goiters The color of the nodules may likewise vary from the pale yellowish pink semi translucent character of a colloid nodule to the grayish pale and opaque appearance of the fetal adenoma Degenerative changes namely hemorrhage cyst formation and foci of calcification are particularly characteristic of nodular goiter and are more common in those of large size and among the fetal adenomas With hemorrhage various shades of red brown or yellow may appear in the nodule Cyst formation occurs through dissolution of the follicles and the cystic contents may comprise remnants of the alveolar tissue clear or gelatinous colloid material and cholesterol crystals

Histologically nodular goiter most frequently will appear either as colloid nodules or as so called fetal adenomas Definite tumors of a benign or malignant nature may present themselves clinically as nodular goiter the macroscopic structure of these nodules will be considered in the section on thyroid neoplasms The colloid nodule consists of a poorly defined fibrous capsule containing colloid filled acini often of huge size and lined by low cuboidal epithelial cells which may be so

flattened as to resemble endothelial cells The follicles toward the periphery of the nodule tend to be smaller than those in the center The smaller follicles may be devoid of colloid Focal hyperplasia of the epithelium is often present

The fetal adenoma was first described by Wolfler [8] in 1883 and was so named because of his belief that it arose from fetal cell rests This term has persisted as a name for a definite pathological picture even though its conceptual basis has been shown erroneous Histologically, such a nodule will show a thin capsule containing colloid and is lined by atrophic epithelium Scattered lymphocytes may appear in the interstitial tissue The nodule is composed primarily of small acini most of them containing colloid and is lined by cuboidal epithelium The acini are widely separated by a loose reticular structure whose meshwork is filled with a pale homogenous pink staining matrix which resembles intrafollicular colloid in its staining characteristics Connective tissue is typically absent

The fetal adenoma bears a close relation to the colloid nodule Rienhoff [3] after a study of wax models of the thyroid gland in correlation with stained serial sections concludes that the so called fetal adenoma is an example of extreme involutional change Boyd [40] makes no fundamental distinction between the colloid and fetal types of adenoma finding that one type shades off into the other and that in a single section both forms may appear The acini of the fetal adenoma may show active budding but no intra acinar projections Finally Murphy and Almquist [41] have demonstrated the histological origin of fetal adenomas from epithelial proliferations within a colloid follicle or body of varying size and without obligate capsulation They ascribe the unusual appearance to the fact that there is intra-acinous proliferation of epithelium into the colloid which supports its growth and obviates the need for connective-tissue support

The future development of this type of lesion may be along one of these courses (1) the acini may function as normal thyroid cells (2) hyperplastic changes may occur with the formation of nodular hyperplastic and hyperfunctioning goiter (3) neoplastic change may develop (4) hemorrhage with secondary necrosis cyst formation or fibrosis may take place

The functional behavior of thyroid nodules has been clarified by Puppel Leblond and by Curtis [4] through study of radioactive iodine and ordinary iodine fractionation in thyroid nodules and in the surrounding thyroid parenchyma These investigators correlated the clinical and pathological picture of nodular goiter with the iodine and radio iodine

fractionation in the nodule and in the perinodular thyroid tissue The iodine fractions were determined as inorganic iodine diiodotyrosine and thyroxine The nodules varied in their histological picture from colloid nodule to fetal adenoma These nodules produced much smaller amounts of physiologically active organic iodine compounds than the surrounding thyroid confirming Marine s earlier work [43] Thus the contribution of the nodular tissue to total thyroid function was small and not at all in relation to its size The hormone producing capacity of nodules found associated with exophthalmic goiter or toxic nodular goiter was similarly much less than that of the surrounding hyperplastic tissue in fact these nodules were functionally autonomous acting like the nodules found in non toxic nodular goiter

The avidity of all these nodules for radio iodine was less than that of the surrounding thyroid tissue This contrasts sharply with the behavior of the rarely encountered hyperfunctioning adenoma of the thyroid which has been shown by Cope and his associates [44] to be more avid for radio iodine than the perinodular tissue Such hyperfunctioning nodules undoubtedly produce more hormone than the surrounding thyroid tissue as evidenced by atrophy of this tissue and cure of the associated thyrotoxicosis by enucleation of the nodule

Symptoms and Signs

The symptoms produced by non toxic nodular goiter depend upon the size and location of the nodule or nodules Location is more important than size for a small nodule that is partly substernal may produce marked pressure symptoms through obstruction of the narrow thoracic inlet whereas a large nodule completely suprasternal may disfigure without producing symptoms The arrangement of the bones muscles and fascia of the neck hinder upward backward and lateral extension of the cervical goiter but do favor anterior or downward growth Gravity and the respiratory movements combined with the lack of containing muscles or fascial planes further aid in the downward propagation of nodular goiter It is for this reason that many cervical goiters have subclavicular substernal or intrathoracic components conversely the substernal or intrathoracic goiter is almost always found to be partially suprasternal If pressure symptoms occur they are similar to those produced by large colloid goiters namely cough dyspnoea hoarseness and dysphagia

The physical findings depend largely upon the stage of the disease Early in the course of the process small nodules may be imbedded so deeply in a diffuse colloid goiter that they are neither visible nor palpable With progressive involution of the surrounding colloid the nodules become more apparent In addition there is a tendency for the nodule to enlarge with age

Nodular goiters are easily recognized by inspection and palpation



A B

Fig 4 L F (B I H No 53561) a 35 year old woman native of Maine with large cystic goiter of 10 years duration and with symptoms and signs of hypothyroidism for 2 years preceding thyroidectomy Thyroidectomy 7/14/40 Pathologist reported involution nodules with cystic degeneration

Asymmetrical enlargement may be seen and felt Single or multiple nodules may be present The consistency circumscription and mobility of the nodule should be carefully noted Calcareous deposits carcinoma or thyroiditis produce extremely hard masses Cystic changes may produce fluctuant translucent swellings Murmurs may be audible in this *latter instance but ordinarily murmurs and thrills will be absent in* nontoxic nodular goiters The essential information sought in the examina

tion is the demonstration of a discrete and circumscribed mass or masses distinct from surrounding thyroid parenchyma the degree of tracheal deviation and compression and the attachment of the mass to surrounding tissues Roentgenography is necessary for the demonstration of tracheal compression and of substernal extension Laryngoscopy will reveal impairment of vocal cord motion due to injury to the recurrent laryngeal nerve (Figs 4 6)

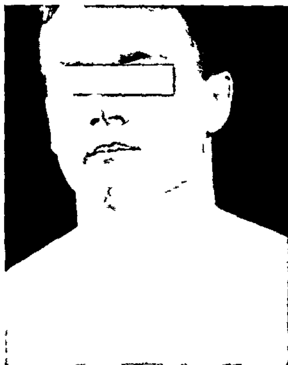


Fig 43 A D O B (BIH No 5 36) Multinodular colloid goiter in a euthyroid boy aged 17 native of Boston with a history of goiter since age of 8 or 9 and recent increase in size with mild pressure symptoms Thyroidectomy on 3 31/49 showed multiple colloid nodules



Fig 43 B Profile view



Fig 44 B D (BIH No 96) 0) a 63 year-old euthyroid woman native of Massachusetts with multinodular goiter of 42 years duration increasing in size and producing pressure symptoms during the 2 years preceding thyroidectomy Thyroidectomy on 10/ 8/47 showed multiple colloid masses in various stages of biological change No malignancy was found

Fig 45 A J G (B I H 88 A) Calcified thyroid cyst in a man aged 5 with cough dyspnoea and dysphagia Postero anterior view showing large cyst with calcified wall displacing and compressing the trachea from the right



Fig 45 B J G (B I H 882A) Oblique view

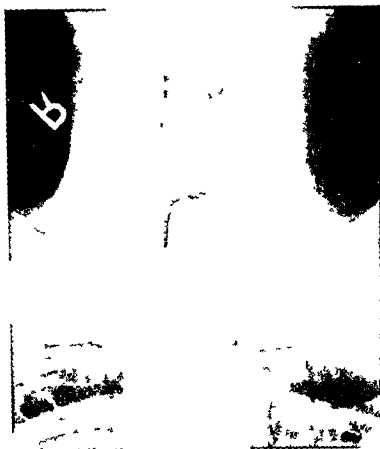


Fig 46 A B (BIH p 48-450l) Nodular non toxic goiter in man aged 59 with cough and dysphagia Postero anterior view of a large ovoid calcified mass to the left and anteriorly to the trachea and esophagus Its lower pole reaches below the jugular notch The esophagus is filled with barium

Clinical Course

The clinical development of nodular goiter may proceed along several courses. The nodule may remain the same for long periods of time, it may grow and press on neighboring structures, it may degenerate or be the site of hemorrhage, it may be neoplastic, either benign or malignant, it may rarely hyperfunction within itself or, more commonly, be associated with perinodular hyperfunction, and, very rarely, it may involute and disappear altogether.

Thyrotoxicosis may develop in patients who have had asymptomatic nodular goiter for many years. In most instances the nodule is an incidental pathological finding in a diffusely hyperplastic gland. In a small number of cases the nodule itself is both hyperplastic and hypersecretory and is surrounded by an involuted or atrophic thyroid parenchyma.[43] Eventually a considerable number of patients with nodular goiters will develop thyrotoxicosis. The incidence of this development varies considerably. Means[4] has reported an incidence of 13 per cent in a series of patients with nodular goiter seen at the Massachusetts General Hosiptal. At the Mayo Clinic, Plummer[46,47] has found that 60 per cent of patients with nodular goiter over the age of 60 had associated thyrotoxicosis, whereas only 5 per cent of those under the age of 30 had a similar association. He also noted that the average duration of a nodule before the appearance of hyperthyroidism was about 17½ years. At the Beth Israel Hospital we have found co-existent hyperthyroidism in 19.5 per cent of 200 patients with nodular goiter.

The etiologic relationship between pre-existing benign nodules and the development of thyroid carcinoma is difficult to establish in spite of the incidence of malignancy in surgically excised thyroid nodules. This subject has been reviewed by us on the basis of the pathological findings in 200 cases of nodular goiter treated by thyroidectomy.[49] In our series 14.4 per cent of solitary nodules were malignant neoplasms and 10.4 per cent of patients with multinodular goiter had malignant thyroid neoplasms (Table vi). A more extensive discussion of the relation of nodular goiter to thyroid cancer will be found in the section on thyroid neoplasms (Part x).

Diagnosis

The finding of one or more discrete nodules within the substance of the thyroid gland is the only requisite for the diagnosis of nodular

TABLE VI

Reproduced from Hermanson L, Gargill S L and Lesses M F Jour Clin Endocrinol and Metabol 195[illegible] xii [illegible]

PATHOLOGY AND INCIDENCE OF CANCER IN THYROIDS WITH SINGLE AND MULTIPLE NODULES

Pathologic diagnosis	Number of cases with	
	Single nodule	*Multiple nodules*
Embryonal adenoma with blood vessel invasion	4	1
Fetal adenoma with blood vessel invasion	1	
Papillary carcinoma	7	8
Epidermoid carcinoma	1	
Scirrhous carcinoma	1	
Giant cell carcinoma	1	
Diffuse small-cell carcinoma		1
Total	15	7
Total cases	[illegible]	

The incidence of cancer of the thyroid in 200 cases of nodular goiter	12.5
The incidence of cancer in single nodules	14.4
The incidence of cancer in thyroid with multiple nodules	10.4

The incidence is calculated from the number of patients and not from the number of nodules

goiter The functional state of the thyroid is determined by the procedures outlined in the preceding Part In addition it is possible to discover the functional state of the nodule itself by means of directional counting with a scintillation counter or a properly designed Geiger Muller counter following a tracer dose of radioactive iodine [49] The thyroid nodule whether colloid or carcinomatous will have a measurably decreased uptake as compared with surrounding thyroid tissue except in the occasional instance of a hyperfunctioning nodule in which case the nodule will show a high uptake and the rest of the thyroid gland a depressed uptake Patients with non toxic nodular goiter will have no signs or symptoms of thyrotoxicosis but occasionally may show evidence of decreased thyroid function Substernal extension should be visualized by roentgenography Pressure from the nodule on neighboring structures may be recognized by noting tracheal deviation and compression as well

as by the symptoms of cough, dyspnoea, hoarseness (from paralysis of the recurrent laryngeal nerve), and rarely dysphagia.

The development or presence of malignancy cannot be determined clinically in most instances. While a history of recent growth may be misleading because it may be due to hemorrhage within the nodule, in general rapid growth is suggestive of malignant neoplasm. Unusual firmness, attachment to neighboring structures, fixation of overlying skin, distention of neck veins and enlargement of regional lymphnodes all point to malignancy. Chronic thyroiditis, whether lymphadenoid goiter or Riedel's Struma, may simulate thyroid cancer, biopsy alone being determinative.

Treatment

It is clear from the clinical course and pathology of non-toxic nodular goiter that benign growth with pressure upon neighboring structures, the occurrence of malignancy and the development of thyrotoxicosis are hazards commonly associated with this type of thyroid disease. Thyroidectomy is clearly indicated for the relief of pressure symptoms. Associated thyrotoxicosis is no longer in itself an indication for operation since other measures are available for the control of hyperthyroidism. The need for thyroidectomy in toxic nodular goiter arises from the clinical uncertainty regarding the pathology of the nodule and the argument for thyroidectomy is in no way affected by the functional state of the thyroid.

Single or multiple nodules of the thyroid unassociated with either pressure symptoms or hyperthyroidism may be subdivided further from the point of view of therapy: (1) those that are probably malignant as determined by a history of rapid growth or unusual firmness and (2) *those that appear clinically benign. In the first group* thyroidectomy is definitely indicated. In the second group thyroidectomy is clearly indicated for the solitary nodules and less certainly for the multiple nodules.

While our own experience has shown the incidence of carcinoma in surgically excised nodules to be about 1.5 per cent (Table vi), we cannot agree entirely with the point of view advanced by Hinton[51] who suggests that thyroid nodules should be treated like nodules in the breast—namely by surgical investigation of all cases. The clinical course of breast cancer is radically different from that of the commoner types of thyroid malignancy in that the former is more rapidly invasive and more frequently metastatic than the latter. Thyroid cancers, especially the

papillary adenocarcinoma may remain locally malignant for many years. Their slowness of growth is such that observation over long periods of time may be necessary to grasp their essential kinship to other forms of cancer. In these circumstances, while thyroidectomy is generally advisable, it may be voided altogether in the aged and in those with short life expectancy because of concurrent disease. It may be cautiously deferred in those with multinodular goiter who will agree to frequent clinical observation. In such patients, desiccated thyroid (U.S.P.) in doses of 0.120 to 0.180 gm. (gr. [illegible] to gr. 3) daily may be given for periods of several months to achieve the occasional disappearance of an incompletely encapsulated colloid nodule. Thyroid medication also may prevent the development of further colloid nodules and will cause regression of perinodular thyroid enlargement.

An adequate operation for benign nodular goiter should consist of either unilateral or bilateral subtotal or total thyroidectomy, depending upon the number and extent of the nodules. Simple enucleation of the nodule or nodules is followed by a relatively high incidence of recurrent nodules. Means[45] for instance has found 1[illegible] times the rate of recurrence after simple enucleation as compared to that after subtotal thyroidectomy. Furthermore, it is certainly inconsistent to operate in a minimal way for possible carcinoma. With single nodules, the contralateral lobe should be exposed and inspected.

All nodules after removal should be immediately sectioned by the surgeon or the pathologist and frozen section examinations should also be made in those instances in which there is capsular invasion or attachment to neighboring structures. The therapy of malignant nodules of the thyroid will be discussed in the section on malignant neoplasms of the thyroid (Part V).

III. INTRATHORACIC GOITER

Intrathoracic goiter is a form of nodular goiter which has extended downward into the thorax. It is a special type by virtue of its anatomical location but has the usual range of pathological changes found in cervical or extrathoracic nodular goiter. The majority of these goiters are partially intrathoracic, lying for the most part below the clavicle or substernally, with a cervical component of varying degree that can be palpated. Completely intrathoracic goiter, lying wholly within the thorax, is rarely seen.

Intrathoracic goiter arises as an extension downward of a nodule in the lower pole of either thyroid lobe The anatomical structures of the neck favor descent of such nodules into the superior mediastinum especially after the upper thoracic inlet has been passed The clinical picture produced is therefore the result of pressure from the mass upon surrounding structures, especially the trachea the great veins, the esophagus and the recurrent laryngeal nerve Occasionally there may be associated thyrotoxicosis and malignant degeneration as with cervical nodular goiter

Dyspnoea and cough are the chief presenting symptoms The dyspnoea may be severe and associated with noisy or stridorous breathing It is due to compression kinking deviation and torsion of the trachea by the substernal mass or masses Wheezing may be present simulating bronchial asthma Nocturnal dyspnoea is also characteristic because of increased angulation of the trachea in the varying positions assumed during sleep Cough ensues because of associated bronchitis and tracheitis Dysphagia is not uncommon owing to compression and deviation of the esophagus but severe dysphagia is uncommon Paralysis of the recurrent laryngeal nerve with attendant hoarseness is rare according to Lahey but it occurred in 13 per cent of the cases in Higgins series [4]

Venous engorgement of the chest and neck usually occurs with large intrathoracic goiters especially those appearing on the right side because of pressure on the great veins particularly the superior vena cava The vessels of the neck may be displaced laterally and forward Edema of the head and neck may be present

The diagnosis may be suggested by the symptoms outlined above and by the finding on direct examination of the upper portion of the intrathoracic mass This can be detected in nearly all cases if palpation is carefully done during deglutition or at the end of deep expiration This is an important feature differentiating these masses from other mediastinal tumors Roentgenography is of course invaluable for the demonstration of an intrathoracic growth but will not always establish a clear diagnosis of its nature

The treatment of intrathoracic goiter is exclusively surgical Removal of large intrathoracic goiters is hazardous when compared with the relative harmlessness of thyroidectomy for cervical non toxic nodular goiter The risks of operation are greater—first by virtue of the location secondly because hemorrhage and resultant surgical shock are commoner and more difficult to control and finally because the patients are usually older with more associated cardiovascular disease For these reasons it is advisable to remove all low lying thyroid nodules which tend

to descend subclavicularly during the course of observation or which are partially subclavicular when first seen (Figs 47 48 49)

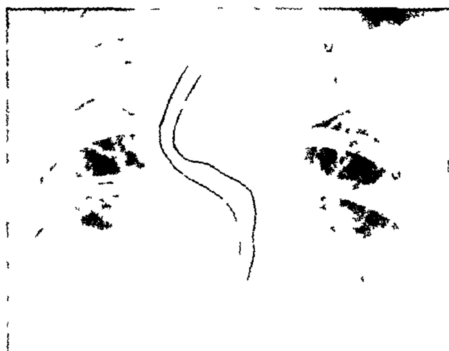


Fig 47 A and B (B I H A1333 ?) Non-toxic nodular goiter in a woman aged 60 with cough and dysphagia Postero-anterior view showing marked displacement to the right and anteriorly of the esophagus (outlined) and trachea by a large mass located mainly to the left and posteriorly and extending two cms below the sterno-clavicular joint





Fig 48 P H (B I H A 567) Substernal goiter in a man aged 61 with cough wheezing dyspnea *Anteroposterior view* showing a large mass compressing and displacing the trachea and esophagus to the right The esophagus is *filled* with barium The mass extends down beneath the *sternum* to the level of the aortic arch



Fig 47 B I B (BIH A13330) Left oblique view with esophagus filled with barium

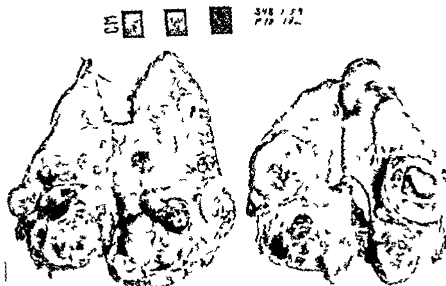


Fig 49 B Appearance of nodules and cysts in cross section of the thyroid Histologically the nodules were hyperinvolution bodies in various stages of biological change many showing hemorrhage and cyst formation None showed malignancy



Fig 49 A Benign multinodular substernal goiter producing severe pressure symptoms successfully removed on 4/ 6/48 from L C (B I H No 098,4) a 6 year old female with acromegaly

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PART VII

TOXIC GOITER

I TOXIC DIFFUSE GOITER

II TOXIC NODULAR GOITER

Introduction

Definition A characteristic clinical syndrome of unknown etiology associated with diffuse symmetrical enlargement of a previously normal thyroid gland a variety of eye changes elevated basal metabolism and increased circulating thyroid hormone The clinical manifestations vary greatly from the florid cases exhibiting all the classical signs of goiter exophthalmos tachycardia and tremor to those with apathy weakness somnolence and muscular wasting without exophthalmos or significant enlargement of the thyroid

Synonyms These are in two groups—eponymic and descriptive Of the former the most widely and justifiably used are the following Parry's disease Graves disease and Basedow's disease or Basedowism The descriptive terms that have been applied include the following exophthalmic goiter hyperthyroidism and thyrotoxicosis

Historical Although Flajani[1] is credited with one of the earliest descriptions his statement cannot be considered as an accurate account of the disease Caleb Hillier Parry however deserves credit for the first recognizable description of this syndrome he apparently considered it a form of heart disease His writing on the subject published by his son in 1825 three years posthumously begins as follows There is one malady which I have in five years seen coincident with what appeared to be enlargement of the heart and which so far as I know has not been noticed in that connection by medical writers The malady to which I allude is enlargement of the thyroid gland This is followed by a report of eight cases showing goiter with tachycardia exophthalmos and edema of seven cases of thyroid enlargement with tachycardia or palpitation and of five cases of thyroid enlargement without heart symptoms

36 MARINI D The pathogenesis and prevention of simple or endemic goiter Jour Am Med Assoc 1935 civ 2334
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this disease This point of view has been upheld by the studies of von Mueller[16] and Aschoff[17] Crotti[18] in fact claimed an even higher incidence of toxic goiter in regions of endemic goiter Sallstrom[19] however reporting from Sweden found no correlation between the incidence of toxic and endemic goiter

In the United States McClendon and Hathaway[20] utilizing data from the U S Army draft records concluded that the geographical incidence of simple and exophthalmic goiter was so similar both occurring in the iodine poor areas of the country that they ascribed both diseases to simple iodine want Their sampling was derived from a male population limited in age and cannot be considered accurate In addition the diagnosis was frequently in error since careful distinction was not made between neurocirculatory asthenia common in army recruits and thyrotoxicosis Read[1] in a comprehensive and well considered study of geographical distribution based his findings on questionnaires sent to large representative hospitals throughout the United States The incidence of thyrotoxicosis in over 400 hospitals in a ten year period was then calculated The average incidence of exophthalmic goiter in 14 million hospital admissions was found to be 0 57 per cent with a range from 0 6 per cent in the southern states to 1 65 per cent in the Pacific northwest Toxic diffuse goiter occurred more uniformly throughout the country than did simple or iodine deficiency goiter although there was a somewhat higher incidence of toxic goiter in the areas of endemic goiter Large urban communities whether in goitrous or non goitrous regions had a particularly high incidence a finding in accord with that of Sallstrom[11] in Sweden

The disease is more common in women the exact ratio between the sexes varying somewhat in goitrous and non goitrous areas usually being about 5 1 in the latter and 5 3 in the former regions No race appears to be immune as typical cases have been reported from every part of the world

The age of onset is most commonly in the third decade regardless of geographical location but it may occur from early infancy to advanced old age Classical toxic diffuse goiter has been described in an infant at *birth* the mother *having had* exophthalmic goiter during the pregnancy[20] and Elliot[3] has encountered it during the first year of life Gardiner Hill[4] studied age incidence statistically and found that women show three peaks of high incidence (1) single girls between puberty and twenty four (2) married women from twenty five to forty two and (3) married women at or about the climacteric

In 1835, Graves[3] of Dublin in the twelfth of a series of lectures incidentally described the syndrome which bears his name. The subjects covered in this lecture were 'Persesquinitrate of Iron in Chronic Diarrhea—Blueness of Fingers and Toes in Fever—Some Account of the Yellow Fever which Prevailed in Dublin in 1827—Newly Observed Affection of the Thyroid Gland in Females. Its connexion with palpitation with fits of hysteria—Erysipelas—Remarks on the Formation of Acidity of the Stomach in Indigestion—Psoriasis—Treatment by Arsenic.' Graves described three cases in females. All had exophthalmos, thyroid enlargement, tachycardia, and palpitation. Loss of weight, emaciation, nervousness, diarrhea, night sweats, and edema were also noted.

Basedow[4] in 1840 also published an early and classical description of the disease, emphasizing particularly the exophthalmos. He ascribed the disease to 'a blood dyscrasia which by reason of some as yet unknown scrofulous taint takes the form of glandular growths and tissue hypertrophy.' Probably the first autopsy in a patient with exophthalmic goiter was performed by Basedow. He also appears to have used spring water rich in iodine for the successful treatment of a severe case of thyrotoxicosis and to have mentioned iodides as valuable in the treatment of the disease.

Trousseau,[5] Charcot,[6] and Marie[7] were particularly impressed by the nervous manifestations of thyrotoxicosis; indeed they considered the disease to have a nervous origin and the thyroid enlargement to be a secondary incident. Mobius,[8] in 1886, first suggested that a pathological thyroid gland was the primary cause of the malady. Subsequently Greenfield,[9] Lubarsch,[10] Stewart and Gibson,[11] Horsley,[1] and Edmunds[12] described hyperplasia of the thyroid as an invariable accompaniment of thyrotoxicosis.

Distribution and Incidence

The geographical distribution of toxic diffuse goiter is not precisely known. It is not a reportable disease and does not have such a high or inevitable mortality that autopsy statistics will yield significant figures on distribution. Estimates of its frequency, therefore, have been derived from clinical impressions garnered from Army draft records dealing with males only, or deduced with some accuracy from the statistics of large urban hospitals. McCarrison[14] found exophthalmic goiter to be rare in areas of goiter endemicity. Kocher,[15] however, reported that in Switzerland goitrous and non-goitrous regions had equal incidence of

Markham[28] first noted hyperplasia of the thymus in the disease and subsequently it has been demonstrated that thymic hyperplasia or regeneration occurs in three fourths of patients under the age of 30 This lymphoid hyperplasia is reflected in the lymphocytosis of the blood which is so common in exophthalmic goiter and also reveals itself in lymphocytic infiltration in the thyroid gland itself Warthin[29] felt that there was a typical Graves constitution which had to exist before the disease could occur and that this constitution was typically characterized by generalized lymphoid hyperplasia Marine[30] has accepted the general idea of a predisposing constitutional type but considers that it may be acquired through various mechanisms especially those wherein sublethal adrenal injury has occurred

Moschcowitz[31] has likewise emphasized the constitutional background as an important factor in the cause of exophthalmic goiter By constitution he means the mental and emotional make up of the patient however rather than any specific physical type The Graves personality according to this concept is that of the sensitive emotional type and it is present before during and after the disease The specific personality type is frequently familial and hereditary Lorand and Moschcowitz[32] in a psychoanalytic study of 50 patients with Graves disease found their sensitivity of temperament explicable on the basis of excessive protection by the mother in early childhood This led to infantile reactions in adult life and an inability to cope with its usual hardships

Current trends in psychosomatic medicine do not stress specific emotional types or hereditary predispositions but do make much of emotional conflicts existing at the time of onset of the disease[33] Conrad[34] found disturbances in the mother child relationship but of a type opposite to that found by Lorand and Moschcowitz[32] for in her series a large number of patients had lost their mothers at an early age others had been unduly imposed with responsible burdens by the mothers In her series psychic trauma was demonstrated in 94 per cent of the cases In reference to this entire subject Joll[35] the English surgeon sagely remarks that it is not possible to estimate the real significance of these factors in the causation of the disease until we know whether a history of worries and emotional strains is more common among those suffering from exophthalmic goiter than among the general population

Shock

In some instances a severe shock or fright may be followed by thyro

Etiological Factors

Though the cause of toxic diffuse goiter is unknown many facts relevant to its pathogenesis are available All theories of causation must be adequate to explain the two striking features of the disease namely the exophthalmos and the hyperfunctioning goiter

Heredity

The hereditary background of exophthalmic goiter has been discussed extensively because of the frequency of multiple cases in the same family Thorough investigations of this aspect of the disease have been published by Bartels [6] and Martin [7] These studies are of particular importance because they are based on careful analyses of relatively large numbers of cases personally investigated by the authors Bartels[76] reported 197 cases of toxic goiter both diffuse and nodular In 69 cases of toxic diffuse goiter a family history of toxic goiter was found in 42 per cent He concluded that there was a recessive Mendelian characteristic responsible for the inheritance of exophthalmic goiter and that this characteristic was partially sex-linked since 70 to 80 per cent of the cases occurred in women

Martin [7] examined 90 adults with exophthalmic goiter and constructed detailed family trees in 35 cases He also simultaneously studied a somewhat larger group of patients with toxic and non-toxic nodular goiter He found that female relatives of patients with exophthalmic goiter were affected 6 times more frequently than male relatives, and that sisters were most commonly involved While male relatives were rarely affected brothers manifested the disease most commonly Finally patients with exophthalmic goiter had more relatives with this disease than did patients with nodular goiter by a ratio of 8 5 1

Martin s statistics when subjected to analysis by Prof R A Fisher, the British geneticist, indicated a qualitative tendency of recessive inheritance rather than environmental influences or inheritance of a dominant type There was no evidence favoring heredity in nodular goiter

Constitution

A characteristic physical or mental constitution predisposing to the development of Graves disease has been stressed by some authors

in iodine deficiency or with thiouracil administration and hyposecretion of the hormone In addition the administration of iodine is quickly followed by colloid storage in the thyrotoxic gland

The hypersecretory activity of the thyroid gland in Graves disease cannot be adequately explained on any known basis of internal abnormality

Role of the Anterior Pituitary

The interrelations of the thyroid and the anterior pituitary have been discussed in Part II The thyroid is largely dependent on thyrotrophin from the anterior pituitary for maintenance of its structural and secretory capacity Thyrotrophin is probably derived from the basophilic cells of the adenohypophysis It produces an increased height of the follicle cells hypertrophy and hyperplasia of the epithelium colloid resorption increased vascularity and enlargement of the gland These are the very changes which are so characteristic of the goiter of Graves disease

Thyrotrophin also causes a decrease in the iodine and hormonal content of the thyroid gland simultaneously with an increase in the hormonal iodine of the blood—Kocher s thyroid diarrhea In addition the pituitary hormone augments the rate of conversion of inorganic iodine into thyroxine The release of thyroid hormone into the blood is controlled by thyrotrophin to such an extent that with adequate stimulation a hormone free thyroid gland can be produced Moreover either thyrotrophin itself or closely associated substances derived from the anterior pituitary have regularly produced exophthalmos in many species of experimental animals The orbital tissue changes in patients with thyrotoxicosis have been found indistinguishable from those produced by injections of anterior pituitary extract

Is thyrotoxicosis therefore a disease initiated and maintained by overactivity of the anterior pituitary This is an attractive hypothesis with an extensive experimental background There are not yet available enough facts to support this idea however In patients with toxic goiter pathological changes *in the anterior pituitary have not been demonstrated* No substantial proof is available of increased thyrotrophin secretion or circulation in exophthalmic goiter much of the difficulty is due to the inadequacies of extant methods of hormone assay Furthermore typical hyperthyroidism is rarely associated with clear cut examples of pituitary overactivity as occur in acromegaly or pituitary basophilism Again if

toxicosis—Schreckbasedow—i.e., Basedow's disease of fright origin. Such cases undoubtedly exist but in many instances in our experience it is difficult to determine whether the acute fright has precipitated Graves disease or has merely aggravated an existent mild case. Traumatic shock cannot be a very significant factor among men at any rate since neither World War I nor II resulted in any great increases in the disease among soldiers or civilians.

Neurogenic Factors

Several authors, particularly Eppinger and Hess,[36] von Noorden Jr.[37] and Kessel, Hyman and Lieb[38] have ascribed toxic goiter to an imbalance of the autonomic nervous system in the direction of excessive sympathetic tone. In terms of modern physiology this idea might be expressed as increased adrenergic activity or decreased cholinergic action. No satisfactory proof has been adduced to support this point of view. Indeed it is well established that thyrotrophin will act on the thyroid quite independently of nervous tissue (see Part II). While thyrotoxic patients and animals may have an increased sensitivity to epinephrin this is far from universal or constant.

Role of the Thyroid Itself

Moebius in 1886[39] and later Plummer[40] have theorized that thyrotoxicosis may be due to the secretion of an altered hormone. Because of the characteristic beneficial effect of iodides in thyrotoxicosis and the greater potency of thyroglobulin derived from thyrotoxic glands Plummer suggested that a less iodized hormone was elaborated and that this hormone was responsible for the symptoms of hyperthyroidism. This hypothesis has been refuted quite convincingly by the work of the bio chemists[41, 42, 43] who have demonstrated the lessened calorigenic activity of thyroxine derivatives containing less iodine. Since Kocher[44] introduced the concept of a thyroid diarrhea as occurring in toxic goiter, and since in fact there occur high levels of circulating hormone associated with low values of gland hormone one might postulate an inadequate storage capacity of the thyroid in Graves disease associated with the continued secretion of normal hormone. There can however be no true loss of storage capacity (i.e. ability to form colloid) in this disease since the hyperplasia of the gland is not distinguishable from that seen

in iodine deficiency or with thiouracil administration and hyposecretion of the hormone. In addition the administration of iodine is quickly followed by colloid storage in the thyrotoxic gland.

The hypersecretory activity of the thyroid gland in Graves' disease cannot be adequately explained on any known basis of internal abnormality.

Role of the Anterior Pituitary

The interrelations of the thyroid and the anterior pituitary have been discussed in Part II. The thyroid is largely dependent on thyrotrophin from the anterior pituitary for maintenance of its structural and secretory capacity. Thyrotrophin is probably derived from the basophilic cells of the adenohypophysis. It produces an increased height of the follicle cells, hypertrophy and hyperplasia of the epithelium, colloid resorption, increased vascularity and enlargement of the gland. These are the very changes which are so characteristic of the goiter of Graves' disease.

Thyrotrophin also causes a decrease in the iodine and hormonal content of the thyroid gland simultaneously with an increase in the hormonal iodine of the blood—Kocher's thyroid diarrhea. In addition the pituitary hormone augments the rate of conversion of inorganic iodine into thyroxine. The release of thyroid hormone into the blood is controlled by thyrotrophin to such an extent that with adequate stimulation a hormone free thyroid gland can be produced. Moreover, either thyrotrophin itself or closely associated substances derived from the anterior pituitary have regularly produced exophthalmos in many species of experimental animals. The orbital tissue changes in patients with thyrotoxicosis have been found indistinguishable from those produced by injections of anterior pituitary extract.

Is thyrotoxicosis therefore a disease initiated and maintained by overactivity of the anterior pituitary? This is an attractive hypothesis with an extensive experimental background. There are not yet available enough facts to support this idea, however. In patients with toxic goiter pathological changes in the anterior pituitary have not been demonstrated. No substantial proof is available of increased thyrotrophin secretion or circulation in exophthalmic goiter; much of the difficulty is due to the inadequacies of extant methods of hormone assay. Furthermore, typical hyperthyroidism is rarely associated with clear cut examples of pituitary overactivity as occur in acromegaly or pituitary basophilism. Again if

an overactive pituitary is the *vis a tergo* in Graves' disease how can we explain the fact that all successful methods for curing clinical thyrotoxicosis depend on either destruction or restriction of the thyroid parenchyma, as with subtotal thyroidectomy or radioactive iodine or on mechanisms for interfering with hormone synthesis, as with thiourea derivatives, or on interference with hormone delivery through increasing colloid storage as with inorganic iodine Iodine is the only therapeutic agent that also exerts an inhibiting effect on thyrotrophin and it is the least certain of available therapeutic methods for accomplishing complete remission

Role of the Adrenals

Marine [50] has stressed the fact that adrenalectomy or sublethal injury to the adrenal cortex results in increased metabolism in animals with intact thyroids This has been confirmed by others (see Part II) Increased metabolism however is only part of the picture of thyrotoxicosis and in the instances where it follows adrenal injury, may be due to effects on the adrenal medulla Epinephrine is highly calorigenic It will produce thyroid hyperplasia through increased thyrotrophin circulation We have seen two instances of thyrotoxicosis in patients with Addison's disease but such cases are certainly exceptional Perera and Porter [5] were able to find only two cases of proved co-existence of Addison's disease and toxic goiter

Miscellaneous Factors

Various miscellaneous factors have received some consideration as causative agents in toxic goiter Infectious agents and infections have frequently been cited as the cause of the disease [46-47] particularly in the earlier literature when the theory of focal infection was in vogue King [4] for example reported a high incidence of tonsillar infection in exophthalmic goiter and believed that tonsillectomy might prevent recurrences *

The ingestion of desiccated thyroid as a factor in the subsequent precipitation of thyrotoxicosis in some cases has been emphasized by the

* Many epidemics of thyrotoxicosis have been reported The Danish epidemic of 1941–5 as described by Meulengracht (Meulengracht E Epidemiologic aspects of thyrotoxicosis Arch Int Med 1949 LXXXIII 119) represents the most carefully documented and analyzed epidemic on record Meulengracht believes that it may have been infectious in origin and asks for an open mind on the possibility of a specific infective agent of unknown nature as a cause of thyrotoxicosis

Scandinavian authors Bruun[45] and Lous[46] The former found that 3 per cent of 485 cases of thyrotoxicosis had been under treatment with thyroid substance for obesity or other non thyrogenous medical ailments shortly preceding the onset of thyrotoxicosis Lous[4] reported nine patients who developed typical Graves disease within six months after they had begun to take thyroid extract In these cases the basal metabolism was known to be normal prior to the initiation of thyroid medication Thyroidectomy was performed in most of these patients and resulted in the finding of hyperplastic glands

Hertz and Means have stressed weight loss as a possible factor in some cases of thyrotoxicosis on the basis of 20 cases of hyperthyroidism that developed following significant weight loss from various non thyrogenous causes including rigid dieting with or without thyroid medication

It is difficult to evaluate the effects of preceding thyroid ingestion or pronounced weight loss as factors in the causation of toxic goiter in view of the commonness of the disease and the likelihood of coincidence

The etiology of toxic goiter is therefore still unknown but the factors most securely established in an important relation to its cause are (1) heredity (2) a predisposing psychosomatic constitution and (3) significant mediation through hormones of the anterior pituitary

Pathology

Thyroid Gland

The degree of enlargement of the thyroid in toxic diffuse goiter varies considerably but in general is slight to moderate never reaching the huge size so often encountered in the non toxic diffuse or nodular goiters Thyroid enlargement may be absent clinically this will be readily understood as the microscopic pathology is reviewed and the distinction between hyperplasia and hypertrophy clarified Hyperthyroidism associated with a completely intrathoracic goiter exhibiting only diffuse hyperplasia without nodule formation is extremely rare but low lying subclavicular or partially substernal glands are not uncommon—these are readily discovered by examination during swallowing

The gross appearance of the toxic gland will depend on previous treatment the occurrence of remissions and occasionally on the acuteness and severity of the disease In the completely untreated case the gland is diffusely enlarged with a finely lobulated almost smooth surface

The consistency is firmer than that of the normal gland, resembling the pancreas On section, the appearance is usually opaque and beefy, uniform in color, contrasting with the translucence of colloid goiter Ordinarily the stroma is inconspicuous but in long standing cases prominent connective-tissue septa develop, giving a distinctly lobular appearance Nodules of varying size may be seen, representing the hyperinvolution bodies of Rienhoff The increased vascularity of the hyperplastic gland is best seen in the operative field rather than on the pathologist's block after draining and collapse of the vessels have occurred Previous administration of iodine alters the gross picture considerably resulting in involution toward the colloid type of gland This is rarely complete so that while the iodinized gland is generally translucent it may contain numerous opaque areas representing non involuted islands of hyperplasia

The microscopic picture of the thyrotoxic gland is not uniform but is ordinarily characterized by changes in the acinar epithelium the colloid the blood vessels and by the frequent appearance of lymphocytic infiltration The exact histology is determined by the balance between hyperplasia and involution, this in turn is dependent on the stage of the disease and previous therapy

Hyperplasia of the thyroid has a unitary pathology but diversity of cause In hyperplasia proliferation of the epithelial cells occurs The cuboidal cell of the normal or resting gland is replaced by tall columnar cells Mitoses, indicating cell division are common The cytoplasm of the cell stains feebly and contains many granules and globules Mitochondria are greatly increased and the Golgi apparatus exhibits changes characteristic of increased cell activity [50] The follicle space enlarges to accommodate the proliferating epithelial cells, which project or papillate into the acinus so that it may become almost solidly filled The colloid representing the stored hormone inevitably alters in appearance staining poorly with eosin becoming vacuolated in the portions contiguous to the acinar cells and frequently disappearing altogether Vascularity is increased and lymphocytic nests may occur These latter changes are more specific in Graves disease and do not necessarily occur as part of the general hyperplastic process

In untreated thyrotoxicosis the picture of hyperplasia presents itself in two general forms Usually there is increased acinar size without increase in the number of acini There is marked papillary infolding of the epithelium which may fill or partially fill the lumen The increased acinar size is not apparent until the involution process causes regression of the papillary buds, thus exposing the increased size of the individual

acinus Less commonly hyperplasia may manifest itself by an increased number of acini of small size lined by very high columnar epithelial cells without papillation into the acinar lumen The changes in the colloid are the same in both types of hyperplasia—it is scanty poorly staining vacuolated and often absent

The stroma of the hyperplastic thyroid gland of Graves disease shows two characteristic changes namely increased vascularity and lymphoid infiltration Warthin[79] considered this latter finding as an indication of the Graves constitution—an obligatory requisite for the development of thyrotoxicosis The degree of lymphocytic infiltration may vary from small collections to definite follicle formation Boyd[5] has found that the use of iodine with establishment of involution increases the incidence of lymphoidosis A similar finding has been reported after the use of thiouracil[53]

The picture of hyperplasia in the thyrotoxic gland is never uniform *even in the uniodinized patient owing to the tendency to involution* which over a long period may gain ascendancy over the hyperplastic process with remission of the disease The process of involution may therefore result from exhaustion of the hyperplastic activity or it may be readily induced by administration of iodine Histologically involu*tion is characterized by enlarged and markedly distended acini lined with* low cuboidal or flattened epithelium and containing within their lumen increased amounts of deeply staining colloid and occasional remnants of papillary projections The fibrous tissue of the stroma is increased while the vascularity is diminished

Rienhoff[54] studied the development of involution in the thyroid glands of patients with Graves disease before and after treatment with Lugol s solution Before iodinization the thyroid showed typical hyperplasia *After iodine had been administered partial complete or excessive invo*lution became manifest Grossly the average involuted gland had lost its smooth surface because of the appearance of nodules of various sizes and cystic areas containing fluid These nodular and cystic areas result from an intensive involution termed hyperinvolution by Rienhoff In the same thyroid gland all degrees of involution co existed Microscopically hyperinvolution manifests itself by abnormally distended acini often of enormous size lined by cells so attenuated that eventually coalescence of several acini into large cavities containing dense colloid occurs This hyperinvolutionary process takes place discretely within the lobule so that large colloid areas develop surrounded by connective tissue Compression and obliteration of surrounding acini occur and the colloid

area surrounded by its capsule of fibrous tissue forms a typical colloid nodule

This sequence of hyperplasia, involution and nodule formation may be repeated many times thus leading to single or multiple nodules The colloid nodule that has evolved from this sequence cannot, therefore be regarded as a true tumor but only as the natural result of hyperplasia regardless of cause Most colloid nodules do not represent a terminal phase of the hyperplasia of thyrotoxicosis but rather of that resulting from the causes of non toxic diffuse goiter already discussed in Part vi Nevertheless it is not rare to find patients with colloid nodules of varying size who present the residual stigmata of a previous pre existent episode of exophthalmic goiter

Pathology of Extrathyroidal Tissues

The treatment of toxic goiter by thyroidectomy has afforded abundant material for extensive study of the pathological changes in the thyroid gland in every stage of the disease and after the use of many therapeutic agents such as iodine thiourea derivatives irradiation and radioactive iodine Knowledge concerning extrathyroidal tissue however has been necessarily derived chiefly from autopsy material This material is meager and in many instances has been obtained from patients dying in acute thyroid crisis This has added terminal factors of metabolic disintegration that may have little to do with the intrinsic pathology of toxic goiter

The available knowledge is concerned largely with pathological changes in the orbital tissues lymphoid tissues including the thymus the liver the muscles the bones and the heart Information is slight with regard to the other endocrine organs such as the pituitary the adrenals and the gonads

Orbital Tissues

The alterations in the tissues of the orbit produced in animals by thyrotrophin have already been described and have been compared to some extent with the changes found in thyrotoxic patients (see Part II) The changes in the eye muscles are part of the generalized myopathy which may occur in thyrotoxicosis as first found by Askanazy in 1898[65] He described interstitial fibrosis with lymphorrhages in voluntary stri

ated muscles and in the extra ocular muscles particularly in severe exophthalmos Mulvany [?] found degenerative changes in the extra ocular muscles indicated by wasting and irregularity of the muscle fibres disintegration of the nerve supply loss of striation granulation of the sarcoplasm and reduplication of the sarcolemmal nuclei The extra ocular muscles may be entirely normal however in thyrotoxicosis when it is not associated with severe or malignant exophthalmos All are agreed [7, 8, 9] that in this latter instance the muscle changes are well marked consisting of chronic hypertrophic myositis with interstitial fibrosis edema and lymphocytic infiltration with frequent germinal centers The muscle hypertrophy is enormous Basedow [4] and much later Smelser [60] have shown that there is diffuse hyperplasia of all the orbital contents particularly of the fat There is also edema fluid present with wandering cells in the fat connective tissue and muscles The edema fluid stains with eosin and anilin blue and is found infiltrating between the connective tissue the muscle fibers and the fat cells Rundle and Pochin [61] have emphasized the increased fat content of the orbital tissues as an important cause of exophthalmos buttressing their contention by chemical analysis of orbits removed post mortem from patients dying with thyrotoxicosis

Muscles

Muscular weakness is commonly present in Graves disease and may though only rarely be associated with severe atrophy of the muscles The exact pathology of the muscles in this disease is not known since few muscle biopsies have been performed Patients dying of thyrotoxicosis however have shown atrophy and degeneration of muscle cells fatty infiltration loss of striations vacuolization proliferation and nuclear degeneration Thorne [7] has reported similar changes in the muscles of patients who have died with so called chronic thyrotoxic myopathy The heart muscle does not show these changes or in fact any specific alteration

Experimentally it has been shown by Paulson [62] that thyrotrophin administered to guinea pigs will produce degenerative changes in skeletal cardiac and ocular muscles These changes are characterized by an initial reaction of diffuse Zenker s degeneration associated with infiltration of phagocytes giant cells and lymphocytes later this is replaced by atrophy and separation of the fibers an increased number of nuclei in

the sarcolemma and lymphocytic collections Dobyns[64] has also noted that thyrotrophin will produce extensive fatty infiltration in the skeletal and ocular muscles as well as in the viscera, and that there is an associated increase in connective tissue in all tissues

Thymus, Lymphoid Tissues, and Bone Marrow

Hyperplasia of the thymus gland is frequently encountered in autopsied cases of thyrotoxicosis It may rarely be demonstrated as a substernal shadow in chest roentgenograms of patients with thyrotoxicosis Generalized lymphoid hyperplasia is even more constantly found with manifestations in the Peyer s patches of the small intestine and in the solitary glands in the large bowel The Malpighian bodies of the spleen show hyperplasia similar to that found in status lymphaticus There may occasionally be slight increase in splenic size and generalized lymph adenopathy

The pathology of the bone marrow in Graves' disease has been well studied by Jones[65] and Bistrom[66] utilizing sternal aspiration Little correlation was found between the bone marrow and the peripheral blood picture The latter is commonly characterized by a lymphocytosis of both absolute and relative proportions moderate over-all leucopenia is frequent In the bone marrow, Jones reported myeloid hyperplasia Bistrom similarly found hyperplasia and a definite increase in the number of young neutrophilic and eosinophilic granulocytes as well as increased numbers of immature red cells He regarded this shift to the left as a form of maturation arrest which ran rather parallel to the severity of the disease and which he ascribed to the high levels of metabolism

Bones

The relation of the thyroid hormone to mineral metabolism has been discussed in Part 1 Extensive and severe decalcification may occur owing to the high calcium losses which are characteristic of thyrotoxicosis This finding is not constant depending on the age of the patient, the duration of the disease, and the dietary intake of calcium and vitamin D

Liver

Patients dying of severe thyrotoxicosis show a high incidence of pathological change in the liver, ranging from fatty infiltration through vari

ous stages of hepatitis and cirrhosis to necrosis and atrophy [6, 59, 61, 70, 71] These changes are not specific and are associated with the varied factors of undernutrition emaciation hypovitaminosis and hypermetabolism which are characteristic of fatal hyperthyroidism

Liver biopsies obtained by aspiration in the course of Graves disease have shown slight and atypical changes [7] even in severe cases indeed the majority showed no anatomical change Clinical and biochemical evidences of hepatic insufficiency are more commonly seen this will be discussed in the section on pathological physiology

Pituitary

In spite of the abundant evidence indicating that the thyrotrophin of the anterior pituitary is an important regulator of thyroidal function as well as bearing a probable relationship to the development of exophthalmos pathological material substantiating these interrelations in human thyrotoxicosis is very scanty The largest autopsied series is that of Holst [72] who reviewed seventeen cases of his own and fourteen cases from other clinics The pituitary was normal or decreased in size never increased The basophils were found degenerated with no constant changes in the eosinophils These findings are consistent with pituitary hypofunction clearly a paradoxical situation in hyperthyroidism emphasizing our lack of knowledge of the etiology of Graves disease

Parathyroids

The excessive excretion of calcium in hyperthyroidism has occasioned interest in the relation of the parathyroids to this process As pointed out in Part 1 there is lack of agreement concerning the presence of hyperparathyroidism in thyrotoxicosis The evidence pro and con has been largely based on clinical or biochemical studies without regard to pathological change in the parathyroid glandules themselves Histopathological studies are important because hypersecretion of the parathyroids is associated with characteristic changes which exhibit themselves as diffuse hyperplasia benign solitary adenoma and rarely as malignant adenoma Little has been published on the subject of parathyroid histology in Graves disease With the assistance of Dr William B Ober we have investigated [73] the material available in our clinic This material consisted of 52 single parathyroid glands removed deliberately or acci

dentally in the course of subtotal thyroidectomy for diffuse toxic goiter All the patients in this series were actively thyrotoxic and had been prepared for surgery with the usual course of iodide therapy None showed clinical or biochemical evidence of hyperparathyroidism In 46 of the 52 cases the single parathyroid gland available was entirely normal In the remaining 6 cases, however, there was variable enlargement of the gland up to twice the normal size, caused by moderate increases in the number of oxyphil cells in the glands One of these 6 cases showed marked oxyphil hyperplasia The significance of these findings is not clear

Pathological changes in the adrenals, gonads, and pancreas are inconstant and not characteristic

Clinical Manifestations of Graves Disease and Their Pathological Physiology

This section will deal with the manifestations of toxic goiter that can be comprehended through clinical examination in conjunction with those laboratory aids which have become an indispensable part of thyroid diagnosis and which may rightly be regarded as extensions of the physician s capacity to see and feel

Goiter

The thyroid gland exhibits moderate enlargement in most instances however there are patients with such slight or minimal enlargement that the goiter may be overlooked The enlargement is symmetrical and diffuse with firmness of the thyroid tissue and clear outline of the borders and lobes The surface is generally smooth or finely lobulated The position of the goiter is that of the normal thyroid occasionally lower, *almost never substernal except when associated with nodules* The size of the gland is not significantly correlated to the severity of the disease The hyperplastic thyroid has increased vascularity, this is manifested by the presence of thrills and murmurs, more commonly found in the superior poles The murmur is usually systolic but may be of the to and fro type with a definite diastolic component Non toxic enlargements of the thyroid or hyperplastic glands which are not hyperfunctioning rarely show murmurs or thrills so that these signs are important in suggesting the diagnosis of thyrotoxicosis

Eye Signs

The ocular changes of thyrotoxicosis are most commonly associated with classical Graves disease rather than with toxic nodular goiter except in those instances where the nodules have resulted from involution of a pre existing diffuse toxic goiter Woods has divided the eye signs of toxic goiter into four general groups as follows (a) lid signs (b) external changes in the lids or eyes (c) extra ocular palsies and ptoses and (d) exophthalmos The lid signs and the external changes in the lids or eyes may occur in non toxic or toxic nodular goiter but are more common *in the toxic diffuse type Extra ocular palsies ptoses and exophthalmos* are characteristic of toxic diffuse goiter

a Lid Signs

1 Dalrymple s sign refers to widening of the palpebral fissure on fixation of the eyes and is caused by retraction of the upper lid It is seen in about one half the cases of toxic goiter It produces the characteristic stare which is frequently mistaken for exophthalmos The retraction of the upper lid does not interfere with closure of the lids

2 von Graefe s sign or lid lag consists of the lagging of the lid behind the downward excursion of the eyeball Occasionally the lid fails entirely to descend as the eye is depressed The lagging descent of the lid exposes a narrow to broad rim of sclera above the cornea Repeated trials may be necessary to elicit this sign Lid lag occurs early in the disease and is found in over three fourths of the cases It is independent of exophthalmos and may be abolished by drugs affecting the nervous system such as morphine

3 Stellwag s sign refers to the infrequency of winking which may occur in thyrotoxicosis It accentuates the staring expression but is not a common sign

4 Joffroy s sign describes the failure of the forehead to wrinkle upon upward rotation of the eyes—the frontalis does not contract concomitantly *with contraction of the levator of the lids*

These signs depend on an imbalance in the opening and closing mechanism of the lids Normally the muscles involved in these processes are the levators of the upper lids innervated by the oculomotor or third cranial nerve which raise the upper lids and the orbicularis oculi innervated by the facial or seventh cranial nerve which close the lids These two muscles normally contract and relax in the synergistic fashion of

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Exophthalmos is always present though it may not be readily apparent unless measured with the exophthalmometer Control of the thyrotoxicosis brings about recession of the paralysis We have seen an instance of this type of palsy in a patient with moderate thyrotoxicosis and an initial BMR of plus 50 per cent The thyrotoxicosis was completely remitted by the administration of potassium iodide with slow but complete disappearance of the ocular paralyses after a period of 2 months Throughout this period the patient was held in a state of latent thyrotoxicosis by the iodide until natural remission had occurred Subtotal thyroidectomy or any other measure that effectively abates the hyperthyroidism will also alleviate the weakness of the eye muscles

The cause of these ocular palsies is not known Though associated with exophthalmos this cannot be the true cause since high degrees of exophthalmos can exist without any paralysis Organic changes in the muscles themselves as demonstrated by muscle biopsy are rare in this group[7]

The second group of ocular palsies are distinguished by the severity of the associated exophthalmos rather than by involvement of the extraocular muscles Brain has termed the condition exophthalmic ophthalmoplegia Jensen[37] has described it as malignant exophthalmos and Means[8] has referred to it as hyperophthalmopathic Graves disease Rundle[7] prefers to call it the ophthalmic type of Graves disease The usual mildness of the associated thyrotoxicosis together with the fact that the syndrome is frequently precipitated by thyroidectomy or more rarely by medical relief of the thyrotoxicosis has led many authors to consider this syndrome as a special and separate kind of Graves disease rather than as a special kind of ophthalmopathy associated with ordinary thyrotoxicosis or as a sequel to its recession To this latter view we ourselves incline for reasons which will be elaborated

Clinically the syndrome is characterized by exophthalmos so marked that the lids cannot cover the eyes adequately There is interference with movement of the two eyes in a particular plane Exposure of the cornea leads to dryness then ulceration and eventually to destruction of the eyeball Swelling of the lids and of the conjunctivae is always present and in fact precedes the exophthalmos Reduced mobility of the eyes incoordination of muscle function epiphora and conjunctivitis are also present The ophthalmoplegia is rarely complete but involvement of the muscle groups that elevate the eyes is common Optic neuritis may occur

As has been noted previously the eye muscles show a characteristic

opposing muscles In addition to these two voluntary muscles there are also involuntary smooth muscles in the upper and lower lids, innervated by the sympathetic nervous system These muscles influence the width of the palpebral fissure

The primary cause of the disturbances in lid closing and opening in toxic goiter is unknown though the lid signs can be simply explained in terms of the muscles involved The Dalrymple sign may be produced by a relaxed orbicularis with compensatory overaction of the levator and hypertonicity of the involuntary lid muscles producing a wide palpebral fissure The lid lag of von Graefe may result from tonic contraction of the palpebral smooth muscles Relaxation or atony of the orbicularis would produce Stellwag's sign An overactive levator with a lack of synergistic action by the frontalis would lead to Joffroy's sign

b External Changes in the Lids and Eyes

Under this heading are included the following (1) weakness of convergence or Moebius' sign (2) abnormal pigmentation of the skin of the lids or Jellinek's sign and (3) excessive lacrimation None of these signs is common or important diagnostically and their mode of production is uncertain

c The Extra ocular Palsies

These occur in about 0 3 per cent of all cases Woods[75] has classified the extra ocular palsies into two groups (1) single or multiple palsies associated with severe thyrotoxicosis and exophthalmos which improve following subsidence of the hyperthyroidism, (2) single or multiple palsies associated with exophthalmos and with mild thyrotoxicosis, which do not subside but in fact become aggravated as the disease remits

There are many exceptions in each of these two groups, in our experience since the first group of palsies may be associated with mild or moderate thyrotoxicosis is not necessarily conjoined with exophthalmos and may not entirely recede after amelioration of the hyperthyroidism The second group of palsies has become known as exophthalmic ophthalmoplegia or as the hyperophthalmic form of Graves disease While it is generally true that the associated hyperthyroidism is mild thyrotoxicosis of moderate or severe degree may be present

The ocular palsies of the first group may affect any of the various eye muscles individually or in groups and may be unilateral or *bilateral* Diplopia and inability to move the eyeball freely are the chief symptoms

or pseudo exophthalmos In relative exophthalmos the eyeball protrudes relative to its previous position but is still in a range that is normal for some individuals In absolute exophthalmos the degree of protrusion is of an order that is abnormal for any eye In normal persons the distance from the external orbital margin to the anterior surface of the orbit is 1 to 16 mm as measured on an accurate exophthalmometer such as the Hertel Myopia per se may cause some degree of exophthalmos Measurements over 16 mm in the absence of high myopia are absolutely indicative of exophthalmos From 16 to 6 mm is the usual range of measurements found in the exophthalmos of Graves disease It is clear that an eyeball which normally protrudes 12 mm and protrudes 14 mm in association with thyrotoxicosis has become exophthalmic by measurement if not by clinical observation The average increase in protrusion of the eyeball in Graves disease is about 5 mm as compared with 7 mm in exophthalmic ophthalmoplegia [8] In false or pseudo exophthalmos the marked stare caused by extreme retraction of the upper lid gives an impression of exophthalmos which is not borne out by measurement with the exophthalmometer In such instances a correct clinical evaluation may often be made by examination of the eyes after gentle closure of the lids

The incidence of exophthalmos in Graves disease varies considerably it is obviously present in at least half of all cases but its true incidence is uncertain because of inadequate examination with the exophthalmometer Very rarely exophthalmos either bilateral or unilateral may be the first manifestation of Graves disease [7] preceding significant elevations of the basal metabolism or other clinical signs however the rarity of this occurrence should be emphasized since ordinarily exophthalmos appears simultaneously with the rest of the characteristic signs and symptoms of the disease Contrary to the general belief that exophthalmos recedes when the hyperthyroidism is brought under control Grace and Weeks [9] and Soley [91] found little or no recession of exophthalmos during a five year period after remission of the thyrotoxicosis Soley [91] in fact found increases of 1 5 mm in exophthalmos after treatment in half of the cases The disappearance of lid lag and stare led earlier observers to the erroneous conclusion that exophthalmos itself had decreased Soley s observations lend further support to the belief that there is an etiological relationship between thyrotoxicosis either present or pre existing and exophthalmos and that depression of the metabolism to normal or subnormal levels tends to increase the exophthalmos

The pathogenesis of exophthalmos in toxic goiter has been discussed

pathology—chronic hypertrophic myositis with fibrosis, edema, and lymphorrhages. These organic changes probably account for the ocular palsies.

The cause of exophthalmic ophthalmoplegia is not known, but the conditions under which it occurs indicate some possible mechanisms of causation. Though it does occur in the course of thyrotoxicosis, it is more likely to be precipitated or become progressive following thyroidectomy[58, 79, 80, 81] or the remission of thyrotoxicosis after treatment with thiourea derivatives.[6] It has been claimed that the syndrome may occur in patients with euthyroid function who have never been thyrotoxic. A critical survey of the reported cases has failed to substantiate this contention in our opinion. Mild hyperthyroidism is readily overlooked, particularly if the basal metabolism is not evaluated; Brain,[78] for example, determined the basal metabolism in only 8 out of his 31 reported cases. Of these 8, 6 had elevated basal metabolisms; 2 were reported as within normal limits but exact figures are not offered. Thyrotoxicosis may be present when the basal metabolic rate is elevated to an extent considered within the normal range by some. Furthermore, the pathological picture of the resected thyroid glands described in Brain's report is not inconsistent with involutionary changes induced by iodides in a hyperplastic gland. An occasional case of spontaneous myxedema has been found associated with malignant exophthalmos,[83, 84] but this has not occurred in our clinic. In fact, myxedema induced in patients with intractable heart disease by total ablation of the normal thyroid gland or through the use of radioactive iodine has not once been followed by exophthalmos in the large series of well over 150 cases studied by H. L. Blumgart[8] at the Beth Israel Hospital in Boston.

Exophthalmic ophthalmoplegia is far more common in males than in females; this is particularly striking in view of the high incidence of exophthalmic goiter in females. Marine[86, 87] found that exophthalmos induced in rabbits by methyl cyanide was more common in young male rabbits and was prevented by castration.

We incline strongly to the view that pre-existent or co-existing thyrotoxicosis is an essential element in the cause of progressive severe exophthalmos and that unknown factors in the interplay between the thyroid gland and the anterior pituitary are largely responsible for the ophthalmopathia of Graves' disease.

d. Exophthalmos

This manifestation of Graves' disease may be seen as relative, absolute

metabolically and clinically The moist warm flushed skin occurs because the hypermetabolism requires the increased elimination of heat This is accomplished through vasodilatation Sensible sweating and insensible perspiration are both increased The skin temperature particularly in the lower extremities is elevated [94] in order to promote heat loss Increased perspiration both sensible and insensible is also a reflection of this same necessity The insensible perspiration representing water vapor from the lungs and skin and carbon dioxide from the lungs is increased proportionately to the basal metabolism [94] The rate of blood flow through the extremities has been found significantly increased in hyperthyroidism [9] The number of patent capillaries has also been found to be significantly greater in the skin of hyperthyroid patients [96] All of these changes are quickly reversed by medical or surgical control of the disease

Subjectively the patient will complain of excessive warmth and increased sweating or these complaints may be readily elicited by questioning There will be preference for cooler weather and varying degrees of heat intolerance or thermophobia Dermographia and urticaria are frequently seen Increased pigmentation is common in long standing cases as is vitiligo which may occasionally be found in combination with an Addisonian type of pigmentation [97] A rare dermal syndrome called localized myxedema or circumscribed thyrotoxic myxedema has been reported by several authors [9, 98] It is characterized by mucinous deposits within non pitting raised bluish yellow rectangular plaques occurring in the lower extremities The condition appears to have no relation to true myxedema It usually occurs after thyroidectomy for toxic goiter although it has been initiated by thiouracil induced euthyroidism and has also occurred during active thyrotoxicosis

Abnormal pigmentation of the nails may occur during thyrotoxicosis with disappearance upon remission [16] Nutritional disturbances associated with toxic goiter result in trophic changes in the nails longitudinal striae may appear and eventually there may be flattening or even spooning of the nails as in marked cases of hypochromic anemia

The hair is characteristically fine and silken in Graves disease but in long standing cases it may be dry and lusterless It usually becomes thinned from excessive falling out

Nutritional State

Maintenance of the body weight depends on a balance between energy

by Woods[75], its relation to thyrotrophin or a related exophthalmic factor in the anterior pituitary has been reviewed in Part II Many concepts have been advanced to explain the exophthalmos Hyperplasia of the orbital contents especially of the fat was first advanced by Basedow[4] as a possible cause of exophthalmos This hyperplasia does indeed exist and is the immediate cause of the protrusion of the eyeball

A second theory ascribes the exophthalmos to overactivity of the cervical sympathetic which produces its effect by contraction of Mueller's orbital muscles In man this muscle covers the superior aspect of the infra orbital fissures and acts to tense the fascia of the floor of the orbit In animals where the muscle is less vestigial, it is conceivable that its contraction could cause exophthalmos In man however, a direct stimulation of the cervical sympathetics under carefully controlled conditions has failed to result in any measurable protrusion of the eyeball[9] In any event this factor cannot be significant in view of Soley's observations[91] on the permanence of established exophthalmos in thyrotoxicosis Orbital hyperplasia obviously cannot result instantly from nerve stimulation

Edema of the orbital contents, dilation of the orbital blood vessels and the occurrence of degenerative myositis with increased muscle bulk have also been advanced as possible causes of exophthalmos None has been convincingly established as the primary factor, though all are present to a degree and may therefore be considered contributory

The theory that the anterior pituitary elaborates a hormone perhaps thyrotrophin or a closely related secretion, which causes exophthalmos is attractive and better substantiated than all others for animals In man however little is yet available beyond theory So we can only agree with Woods[7] in his final conclusions, as follows

The problem is still unsolved Exophthalmos is probably not related directly to thyrotoxicosis and not at all to sympathicotonia Both thyrotoxicosis and exophthalmos are related in some way to the action of anterior pituitary hormone The means by which it accomplishes this end is still a mystery Muscular action probably cannot pull or push forward the eyeball Orbital hyperplasia and edema with myositis are present but it is not clear whether these changes are primary or follow displacement of the eye Once initiated however this orbital hyperplasia persists and may progress despite control of the thyrotoxicosis

The Skin, Nails, and Hair

Changes in the skin are of particular importance in toxic goiter both

conserving mechanism does not operate and the basal metabolism remains high or may even go higher If inadequate calories are ingested weight loss occurs this weight loss necessarily represents combustion of body tissue first available carbohydrate then surplus fat and finally protein In thyrotoxic patients who have lost or who are losing weight respiratory quotients of about 0.75 will be found indicating that the body is consuming its own fat depots to supply the total calories demanded by the organism

The caloric requirements for weight maintenance in toxic goiter *may be enormous and are usually proportional to the basal metabolism* Boothby and Sandiford [1] as well as Sturgis and Greene [101] have estimated that the total energy requirement may be as high as 100 per cent above the basal level in contrast to an average increase of 50 per cent in normal persons What this means in calories for a 24 hour period may be readily seen from the figures of Boothby and Sandiford [10] who showed that in thyrotoxic patients at rest in bed a 24 hour caloric intake of 3517 calories was necessary for weight maintenance or slight weight gain an intake 90 per cent greater than the average basal caloric requirement in euthyroid subjects

Jones [104] in a study of self selected diets in various diseases has demonstrated that patients with toxic goiter uniformly tend to select a diet rather low in protein and high in carbohydrate Nutritionally this type of selection may be harmful but metabolically it may be justifiable since *it represents another way* of reducing the specific dynamic action of food which resides largely in the protein fraction

Cardiovascular Manifestations

The cardiovascular manifestations of toxic goiter are palpitation tachycardia dyspnea arrhythmias increased blood pressure overactivity of the heart various physiological murmurs cardiac enlargement and heart pain These symptoms and signs are largely due to the alterations in cardiovascular physiology caused by excessive thyroid hormone Autopsies of patients dying from hyperthyroidism have shown no characteristic lesions mostly the hearts are normal except where there has been co existent heart disease [3] particularly rheumatic and coronary heart disease Although McEachern and Rake [10] feel that hyperthyroidism can cause cardiac hypertrophy Hurxthal [106] found normal sized hearts by roentgenography except where there was coincident cardiovascular

taken in as food and energy expended through the oxidative processes that make up the basal metabolism plus increments of varying size produced by work specific dynamic action of foods and changes in temperature Regulation of the amount of food ingested depends on the appetite whereas the regulation of energy expenditure depends initially on the level of the basal metabolism In toxic goiter the nutritional state is significantly altered because there is on the one hand a marked increase in appetite and on the other hand, slight to marked increases in the basal metabolism These factors are opposed in their physiological effect but in this disease the appetite fails to maintain the body weight in the face of persistent and increasing elevations both in the basal and total metabolism

The increased appetite so characteristic of thyrotoxicosis is not so apparent to the patient as to the family and friends who notice the excessive consumption of food If questioned the patient readily admits the increase of appetite but rarely offers it among the chief complaints Anorexia occurs in very ill patients particularly in those on the verge of crisis but may be seen in any phase of the disease Sturgis and Greene[101] found moderate to marked increases in appetite in 55 per cent of their cases a normal appetite in 33 per cent and a decreased appetite in the remaining 12 per cent This analysis indicates that in at least one third of the cases the patient had not been aware of subjective changes in the desire for food

Weight loss in toxic goiter is one of the commonest symptoms noticed by the patient The factors involved have been studied by Boothby and Sandiford[10] and by Sturgis and Greene[101] A normal person will have a total caloric need about 50 per cent above the basal caloric requirement This is represented chiefly by muscular exertion and to a smaller extent perhaps 10 per cent, by the specific dynamic action of food In toxic goiter however there is present in addition the factors of body tremors inefficient utilization of muscular contraction in work[101] and a considerable increment in the percentage of calories ascribed to specific dynamic action of food because of the large food intake When these extra burdens are superimposed on the higher level of basal metabolism which obtains in the disease it is apparent that the maintenance of normal body weight is difficult and usually impossible either when the disease is moderate or severe or when it is mild and protracted

Weight loss and undernutrition in euthyroid persons will result in quite marked reduction in the basal metabolism—which tends to counteract further decreases in weight In thyrotoxic individuals, however this

brought about by the increased volume output of the heart the decreased diastolic pressure results from the peripheral vasodilatation characteristic of the disease

The *increased pulse rate and pulse pressure* together with the flushed warm moist skin indicate that the rate of blood flow is increased in toxic goiter The minute volume output of the heart in thyrotoxic patients at rest corresponds to that in normal individuals doing light work [116, 117, 118, 119] In general the basal cardiac output is proportional to the basal metabolism in hyperthyroidism increases of from 50 to 100 per cent may therefore be found A contributory factor in the production of the increased output may be the rapid flow of blood from the arterial to the venous side through widely dilated thyroid vessels characteristically found in the hyperplastic gland of Graves disease Rynearson and his co workers [120] found an oxygen saturation characteristic of arterial blood in both the thyroid artery and vein in thyrotoxicosis indicating an extremely patulous capillary bed in the gland itself allowing rapid passage of blood A similar condition prevails in the peripheral capillary bed so that in hyperthyroidism the increased work of the heart is expended chiefly upon the increased frequency of the pulse rate rather than in overcoming mechanical obstruction to the flow of blood Yater [121] believes that this reduced resistance in the peripheral capillaries to blood flow explains the infrequency of heart failure and cardiac hypertrophy in spite of the increased cardiac work which obtains in toxic goiter

Blood volume itself is increased in thyrotoxicosis according to Gibson and Harris [122] The velocity of blood flow or the circulation time is markedly accelerated both in the systemic and the pulmonic circuits This has been amply demonstrated by the employment of objective tests as in the radioactive deposit method of Blumgart and his co workers [123] or by the use of a variety of tests utilizing subjective end points after injection of such drugs as sodium dehydrocholate [124] and calcium gluconate [125, 126] The increased velocity of blood flow in toxic goiter is probably one of the responses to the needs created by an elevated metabolism

The *heart is characteristically overactive* in Graves disease This is manifested by the forceful and diffuse cardiac impulse the increased intensity of the heart sounds and the presence of physiological murmurs The slapping and prolonged character of the impulse frequently gives the impression of an early systolic thrill An accentuated first sound at the mitral area and a loud second sound at the pulmonic area are usually found with thyrotoxicosis The mitral first sound is not only loud but

disease Friedberg and Sohval[107] in their series of 27 autopsied cases of Graves disease found that cardiac hypertrophy was uncommon in uncomplicated thyrotoxicosis and that when present it was of slight degree Cardiac dilatation, however may occasionally occur and will be marked if there is heart failure

The direct action of thyroxine on the heart muscle is responsible for much of the disturbed cardiac physiology Lewis and McEachern[10] showed that the isolated hearts of thyroxinized rabbits continued to beat at a faster rate than similar preparations from normal animals Andrus and McEachern[109] and Yater[110] confirmed these observations and found that the accelerated rate might persist for hours to days after withdrawal of thyroxine Similar findings in the dog have been reported by Priestley Markowitz and Mann,[111] who transplanted the heart of a small dog into the neck of a larger animal and demonstrated marked acceleration of rate in the transplanted heart from injected thyroxine

Palpitation is one of the most frequent presenting symptoms of thyrotoxicosis but because of its subjective nature is of less diagnostic significance than tachycardia Consciousness of heart action in thyrotoxicosis is due not only to tachycardia but also the increased force of the heart beat the widened pulse pressure and increased cardiac output

Pulse rate in toxic goiter generally parallels the basal metabolism This correlation is more exact when the pulse rate is determined under resting basal conditions Means and Aub[11] noted a parallelism between the pulse rate and the metabolism in hyperthyroidism Sturgis and Tompkins[113] found a similar correlation in a study of 154 patients with toxic goiter and concluded that resting pulse rates below 80 were rarely associated with an increased metabolism A study of their figures however indicates many exceptions to this trend It has been our experience also that resting pulse rates below 80 may occur in toxic goiter of mild or moderate degree The tachycardia of thyrotoxicosis persists during sound sleep[114] unlike tachycardias ascribable to psychogenic factors

Pulse pressure is increased in thyrotoxicosis chiefly as a result of a moderate elevation of the systolic blood pressure and a slight lowering of the diastolic component[11] Patients in the older age groups may have arterial hypertension associated with their hyperthyroidism In such instances the effect on the pulse pressure is similar to that which occurs in thyrotoxicosis unassociated with hypertension Control of the hyperthyroidism usually results in lowering of the pulse pressure due to a decrease in the systolic component and a slight elevation of the diastolic pressure The increase in systolic blood pressure in toxic goiter is

Transient heart block either complete or with marked prolongation of the auriculo ventricular conduction time has been reported in association with toxic goiter This is a rare manifestation for not over a dozen cases have been reported [130] but its probable relation to excessive thyroid hormone is indicated by the reported development of transient complete heart block following the ingestion of large doses of desiccated thyroid [131]

These cardiac disturbances are similar to those observed during the course of acute infections particularly with regard to their paroxysmal nature and the reversion to normal with control of the toxemia or infection Cardiac hypertrophy is rare or slight indicating that overwork of the heart is not the sole factor causing these disturbances although in thyrotoxicosis there is increased cardiac work A toxic factor perhaps the direct effect of excessive circulating thyroid hormone is probably of great importance in their etiology

Dyspnoea is not commonly presented as a symptom of uncomplicated thyrotoxicosis but is readily acknowledged when the patient is questioned It is due both to the reduced vital capacity that is characteristically found in Graves disease [133 134 13] and to the large oxygen needs of the tissues

Neuromuscular Manifestations

Nervousness irritability restlessness increased fatigability tremors and muscular weakness are common complaints in toxic goiter

The *nervousness* of Graves disease is more apparent to the observer than to the patient It is not uncommon for the patient to feel overly optimistic even euphoric and to deny nervous symptoms However many are irritable react quickly with excessive tears or laughter to trivial stimuli and on observation present a picture of mild to severe agitation There is loquacity and rapid almost eruptive speech The patient is restless carries out many unnecessary movements usually jerky and unco ordinated but purposeful and associated with considerable tremor of the hands sometimes of the entire body Though appearing to be emotionally labile the patient often exhibits a great drive and desire for work which cannot be accomplished with facility because of the increased fatigue that is characteristic of the disease Most patients are exceptionally intelligent and anxious to co-operate but frequently show poor judgment and lack of appreciation of the degree of their illness Cerebral activity is increased and insomnia is common

snapping in quality and simulates closely the final component of the late diastolic crescendo murmur of mitral stenosis

Cardiac murmurs are common and are generally of two types both systolic in time (1) a blowing systolic murmur of variable intensity which accompanies the first sound, lasting through part or all of systole heard at the mitral area with a variable transmission toward the axilla depending upon its loudness, and (2) a blowing systolic murmur localized at the third left intercostal space Both these murmurs disappear with remission of the thyrotoxicosis When the mitral systolic murmur is loud, transmitted toward the axilla and associated with a snapping first sound the diagnosis of mitral stenosis and regurgitation may strongly suggest itself Indeed structural disease of the mitral valve cannot be excluded in such instances until the thyrotoxicosis has abated Diastolic murmurs of the heart have not occurred in our experience but Eason[177] has described a faint early diastolic murmur along the left border of the sternum which he considered of functional origin

The diagnosis of coexistent heart disease although difficult at times must be made as early as possible because of the deleterious effect of even mild thyrotoxicosis upon a damaged heart When the diagnosis cannot be made because of the equivocal nature of the murmurs, other considerations such as heart size associated hypertension or coronary heart disease and the presence of persistent auricular fibrillation and congestive failure will be helpful in establishing the diagnosis of heart disease

Disturbances in *cardiac rhythm* occur commonly in toxic goiter These comprise sinus arrhythmias extrasystoles paroxysmal tachycardia, paroxysmal or persistent auricular fibrillation auricular flutter, and heart block The most frequently encountered arrhythmia is auricular fibrillation with an incidence of 15 to 25 per cent Paroxysmal fibrillation is more characteristic of thyrotoxicosis but persistent fibrillation may become established in the older age groups or when there is associated heart disease Occasionally it may be an early and marked manifestation of hyperthyroidism appearing in paroxysmal form while the disease itself is mild or not clearly apparent[178] yet in other cases permanent fibrillation may precipitate heart failure of such degree as to obscure completely the underlying thyrotoxicosis[179] Transient fibrillation may be provoked by acute infections or by surgical procedures occasionally serving to direct attention to a previously overlooked toxic goiter

Auricular flutter occurs in rare instances and is usually transitory In the few cases reported there has been no evidence of associated heart disease[178, 179]

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INTRODUCTION

History — According to Riley the term hemicrania half the head was introduced by Galen in the first century after Christ In English the term lost first the h and later the ' e becoming megrim or something like that spelled in some twenty different ways, see *Oxford English Dictionary* Migraine is the French form of the word

The man in the street usually calls it sick headache", "bilious sick headache' or blind headache There is mention of the "sick eyed and sick headed in the ancient story of Enki and Ninhursaga written in Mesopotamia some 3 000 years before Christ

Aretaeus of Cappadocia gave perhaps the first clear description of the disease, migraine, about 200 A D He spoke of ' deep-seated pain in the eyes , of ' nausea vomiting torpor heaviness of the head and anxiety So truly he said the patients ' flee the light — their sense of smell is vitiated — they are weary of life and wish to die

Definition — Migraine is a hereditary disease of the brain and the autonomic nerves It is an entity The sick headache is due to a storm ' which seems often to start in the visual center and then to spread perhaps to the vagus center and down into the abdomen where it tends to reverse peristalsis in the duodenum and stomach The storm spreads also to the cervical sympathetic ganglia which cause some of the arteries supplying the surface of the brain to dilate With this the blood goes pounding through them to produce a severe throbbing headache often on one side of the head often with nausea sometimes with vomiting and in all bad cases with great misery and utter prostration

In many cases there are other bizarre manifestations of the storm such as a feeling of coldness all over numbness giddiness slight mental confusion pa es thesias weakness of muscles abdominal distress and rarely, unconsciousness Occasionally a patient will have a scotoma without headache a headache without nausea or vomiting or abdominal pain or distress or mental hebetude and depression without a headache

In the case of older persons the story may be that there was 'cyclic vomiting in childhood typical migraine with headache during middle age and abdominal pain without much if any headache in the later years of life The important point to remember is that migraine is a lifelong tendency that is so built into the body and personality of the patient that one cannot hope to eradicate it in any way

One of the most important points to be remembered is that *the headache is only one manifestation of the disease* and oftentimes only a minor one Much more distressing to the victim is usually a physical frailness a frequent sickliness an easy fatigability and an inability to stand up to any strain or excitement

The Migrainous Personality

The migrainous personality is distinctive The migrainous woman the patient is perhaps three times more likely to be a woman than a man is often trimly built and well dressed intelligent wide awake bright eyed overly sensitive tense and quick in her thinking and her movements Someone has called migraine a disease of the alert mind

It is very helpful to recognize the type of person and then to ask about migraine because so many of the victims of the disease fail to mention that they have or have had sick headaches and without this extremely important fact the only diagnosis the physician may be able to make will be that of a neurosis or functional disturbance But once he knows that the patient is migrainous the nature of the whole syndrome and lifelong illness may become clear and he can then draw out the rest of the story With the new information he will see why the woman has always been sickly frail easily tired and often faint and a bit dizzy Knowing also the common curses and mental sins of the migrainous person he can quickly draw out the essential story of strain and tension and perhaps dissatisfaction at home and once he has all this information he will no longer feel much need for examining the woman from head to foot he will no longer have to search for the cause of her trouble Better yet if his examination does reveal gallstones or a myomatous uterus he will know that these are not responsible for the syndrome and that their removal will not make the patient over into a strong well person

Usually the woman is a perfectionist who works fast and accurately and likes to hurry other persons along to work fast with her Anything out of the ordinary routine is likely to upset her and bring on a headache She must not shop too long and she must avoid crowds noises bright lights glares and smells She is usually so sensitive to light that the physician must suspect migraine the minute a woman comes in and starts shading her eyes and blinking at his office window

The greatest curse of the migrainous woman is her easy fatigability which apparently is inborn often it comes in girlhood before the headaches and it persists in later life after the headaches have gone Characteristic of migrainous fatigue is the suddenness with which it overwhelms the victim Often the woman gets tired from putting too much emotion and concern into little things Perhaps as a result she sleeps poorly Her desire for perfection causes her to overwork Her house must be spotlessly clean and run just so She hurries and tries to do several things at once or she gets tense just contemplating the work that remains to be done Because her relatives so respect her ability and her judgment and skill in getting things done they all go to her with their problems and sorrows and these burdens wear her down

The migrainous woman gets tense from just thinking of doing something

Typical is her inability often to give a dinner party without getting sick over the mere planning and preparing for it. Because of the great tenseness of the nuchal muscles many sick headaches start at the back of the neck.

Migraine in Men

The migrainous man often has much the same temperament as has the migrainous woman. Almost always he is a brain worker and often a professional man or an artistic idealistic type of person. His great advantage is that, if he lives sensibly and is not psychopathic, he is likely to be about over his troubles by the time he is thirty five.

The Migrainous Physical Make-up

No careful anthropologic study has yet been made of the migrainous man and woman. Ulrich who studied 500 cases reported many physical abnormalities but she did not have a control group. Moehlig's (1931) figures suggest an average build. The writer's impression is that many migrainous women are short, nicely built and feminine in appearance. As Ahrens (1930) noted, they are often of asthenic type. Many are constitutionally inadequate with defective pelvic organs which are removed surgically rather early in life.

Features of an Attack

Liveing's description of migraine is so good that it is well worth repeating. A young woman in the enjoyment of otherwise excellent health, while well nourished, cheerful and active, the life perhaps of her family circle, appears in the morning, once in every two or three weeks, an altered being, with a pale inanimate face, dull lusterless eyes, and with all her usual cheerfulness departed — and so remains through the day in a state of chronic nausea and corresponding mental and bodily dejection, to which use alone has made her resigned, and yet the following morning she will be her former self again as if nothing had occurred, and thus she may continue to live two distinct lives, as it were, perhaps for a long series of years.

Warnings of an Attack

According to Elliot (1935) some 37 per cent of patients have some sort of warning of a headache several hours before it appears. Some feel unusually wide awake and well the evening before and they may then be very talkative, or they may have a big appetite. One woman, for three days before a headache, always

had an abnormally large appetite Others feel rotten' the day before and some have visual disturbances This sort of thing suggests the presence in the body or brain of some sort of chemical tide preceding a headache Sometimes the spouse knows the signs and can tell that an attack is coming Sometimes the breath gets bad

The Scintillating Scotoma

In perhaps 40 per cent of the cases the headache is preceded by a scintillating scotoma As Charles Singer pointed out it was described and pictured in the 12th century by the famous Abbess Hildegarde of Bingen It was well described again in 1778 by C H Parry As he said (quoted from Liveing) After violent fatigue more especially when accompanied with fasting for eight or ten hours I have frequently experienced a sudden failure of sight The general sight did not appear affected but when I looked at any particular object it seemed as if something brown and more or less opaque was interposed between my eyes and it so that I saw it indistinctly or sometimes not at all Most generally it seemed to be exactly in the middle of the object while my sight comprehending all around it was as distinct as usual in consequence of which if I wished to see anything I was obliged to look on one side At other times though much more rarely the cloud was on one side of the direct line of vision After it had continued a few moments the upper or lower edge — I think always the upper — appeared bounded by an edging of light of a zig zag shape and coruscating nearly at right angles to its length The coruscation always appeared to be in one eye but both it and the cloud existed equally whether I looked at an object with one or both eyes open When I shut both eyes covered them with my hands so as to exclude all rays of light the coruscation was still perceptible in the same place and what had been a semi opaque cloud appeared lighter than the rest Parry went on to say that the scotoma would remain for from twenty minutes to half an hour As in the case of quite a few men the scotoma was never followed by a headache

This is a good description of the scotoma as experienced often by the writer and by patients who have described it to him Colored pictures of a scotoma taken from an article by Hubert Airy are to be found in Liveing s book Other fine illustrations are to be found in Gowers Bowman lecture for 1895 He got them from an artist who drew a book full of them showing his own scotomas More pictures are to be found in Jolly s (1902) long article It is a remarkable fact that in the case of many persons such a scotoma lasts always from twenty to twenty five minutes In the case of the writer the disturbance begins with a little blurring of vision with perhaps a bright spot then usually comes the scotoma which for ten minutes builds up in density It does not remove central vision

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to the writer's statistics only some 37 per cent of persons have a true scotoma *with a big blindspot and fortification figures at the beginning of a spell* This agrees well with Elliot's report of 35 per cent

Engel Ferris and Romano (1945) found in electroencephalograms taken during scintillating scotomas signs of abnormal electrical activity in the occipital cortex on one side

The Headache

The main feature of a typical attack of migraine is the headache which is commonly so severe that it is not helped by the taking of any amount of acetyl salicylic acid or other drug of similar analgesic power The pain commonly begins over one eye and later moves over the head In a few persons it always comes on one side as on the right or on the left in others the side affected shifts from attack to attack and in some the ache is bilateral or it begins in the nuchal region In bad cases the pain may run down into the neck

Usually the headache is throbbing in nature but a few patients describe it as suggesting the pressure of an iron ring great distention within the head the strokes of a hammer or the boring of an auger The scalp is likely to get so sensitive that touching the hair is painful Each hair may feel like a needle and movement of the eyes may hurt

Usually all sensations are heightened there is often photophobia and the patient wants to get into a darkened room Sounds pound in on the brain and smells become distressing The patient usually gets so hypersensitive all over that she cannot stand being touched She wants to be left alone and sheltered from all stimuli Events that take place during the attack may not be remembered later With the headache there usually go marked misery and prostration so distinctive that one glance at the apathetic sick looking glassy-eyed person is enough to make the diagnosis

With a typical headache there will go nausea and perhaps vomiting Sometimes patients will say that after some bile comes up they get relief That is why they and some physicians think the liver is at fault In the worst cases the patient will vomit for several days Even when there is no nausea or vomiting the patient will probably not want to eat anything and if anything is put into the stomach it is likely to remain there or in the duodenum for hours The finding of this stagnation by a roentgenologist sometimes leads to the performance of a needless and futile gastroenterostomy or duodenojejunostomy Other symptoms that may go with a headache are feelings of coldness (in perhaps 57 per cent Elliot 1935) numbness in perhaps 20 per cent feelings of uncertainty on standing salivation or dryness of the mouth sweating and rarely diarrhea or frequent urination

but it often makes reading difficult as Parry said, one seems to be looking around the scotoma This is shown by Gowers who pictured a sheet of newspaper with parts blotted out as it is seen by a person with a scotoma As the brown spot gets more dense the curved zigzag line off to one side builds up in brightness and pulsates rapidly not with the heart beat Then, during ten more minutes, the phenomenon fades and vision returns to normal

The uniformity of appearance of this scotoma, as it is described by many persons suggests that its features are dependent on something in the structure of the brain and the constancy of the twenty minute duration suggests that some chemical process builds up and then fades away Actually Lashley (1941) concluded that a scotoma must arise in a wave of intense chemical activity spreading over the visual cortex at a rate of 3 cm a minute He thought he could correlate the phenomenon with the histological structure of the cortex as it is now understood Jolly (1902) reasoned that the disturbance probably originates not in the cortex but in the optic tracts the region of the external corpus geniculatum or even in the chiasm

That the eye need have nothing to do with it was shown by the fact that Raullet s migrainous woman continued to have luminous phenomena after her optic nerves had been destroyed by tabes dorsalis (Paris thesis 1883) That the eye has something to do with it is suggested by the fact, noted by the writer that his luminous fortification figure moves with movement of the eyes Some writers state that the scotoma appears on the side opposite that where the head ache comes and this should tell something about its origin

According to Schumacher and Wolff (1941) and others the scotoma probably is produced by constriction of arteries in the brain This would explain other phenomena sometimes observed at the beginning of headaches phenomena such as transient paralyses numbnesses aphasias and disturbances in thinking Much in favor of this idea of angiospasm were the studies by Dr Cahan on his own scotoma (reported by Schumacher and Wolff 1941) If he took just enough amyl nitrite to flush his face but not enough to lower his blood pressure, his vision cleared

With the scotoma present retinoscopy usually shows little change in the back of the eye (Schultze 1922) Some have reported constriction of the vessels during the stage of the scotoma and dilation afterward during the headache (see Mollendorf (1867) Richter (1935) Paton and others

Many migrainous persons (77 per cent according to Elliot 1935), when asked about a scotoma speak of other visual phenomena such as momentary flashes of light which come during the headache Some speak of blurred vision or ' many black spots' It is hard to say if such minor manifestations during an attack are typical of migraine or if they have diagnostic value Slight and Morrison (1940) encountered visual disturbances in 57 per cent of migrainous persons According

Migrainous Equivalents

There are a number of troubles which come to migrainous persons which appear to be equivalents

Abdominal Pains — At the head of the list of migrainous equivalents should go some peculiar attacks of abdominal pain for which no organic cause can be found Suspicious will be the fact that the first of the spells came when the person was under severe nervous pressure or subject to much annoyance Perhaps it will be learned that they still tend to come when the patient is tired or upset Very suspicious always is the story that at the beginning the interval between attacks was from six to twelve months but that later this shortened until perhaps in the end the spells came every day Sometimes these spells are associated with headache and sometimes they are not

Strongly indicative of a functional trouble is the fact that the patient has had severe attacks of abdominal pain for perhaps years without coming to any bad end This rules out carcinoma and makes it unlikely that there have been recurrent intestinal obstructions The fact that the bowels always move perfectly will tend also to rule out an obstructing lesion in the intestine In these cases the coming of the pain has no relation to meals or anything else except perhaps an emotional storm When digestion is perfect between spells this suggests strongly that the cause of the pain is not a lesion in the digestive tract In attacks it may be noted that the abdominal wall is soft the temperature may remain normal or almost so the leukocyte count will not go up much if at all no extra bile will appear in the blood and no blood cells will show up in the urine

Usually in these cases by the time the consultant sees the patient the appendix and gallbladder have been removed and a careful exploration of the abdomen has failed to reveal any disease These facts will help in making the diagnosis Very helpful also in the diagnosis will be such facts as (1) that the patient is migrainous or comes of a highly migrainous family and (2) that in the past the patient had spells of cyclic vomiting or migrainous headaches and then got over them Sometimes on thinking back the patient will remember that at a certain time the headaches disappeared and apparently were replaced by the abdominal pains Some of the literature on this subject was summarized by Blitstein and Brams in 1926

Pseudo-angina — Fitz Hugh (1940) and others have thought that in many cases a pseudo-angina pectoris or a dull ache in the region of the left nipple is a migrainous equivalent and they may well be right The fact that the ache has nothing to do with effort shows that it is not due to heart disease

Paroxysmal Tachycardia — There is no doubt that paroxysmal tachycardia occasionally afflicts migrainous persons but it is not certain that it shows up in them more often than in the non migrainous Critchler and Ferguson (1933) and

Twilight Spells (Dämmerzustände Dysphrenia Hemicranica Transitoria)

The typically migrainous woman has 'dark days' in which she is a bit depressed, apathetic, dazed or confused, uncommunicative, disconnected from the world about her and miserable, much as if she were in a migrainous attack without the headache or nausea. In such spells she usually has little desire for food or ability to eat it. She may be able to do some work, but she pays little attention to those about her. It is helpful diagnostically to get the patient to tell the story of such days.

Other Interim Discomforts of the Migrainous

Among the interim discomforts of migrainous persons are paresthesias, pains and aches all over the body, a feeling of being swollen all over, bloating, fainting, dizziness or lightheadedness, a sore overly reactive bowel, occasional short spells of nervous diarrhea, asthma, hay fever, paroxysmal tachycardia, frequent urination, excessive perspiration during excitement, vasomotor storms and neurodermititides.

In women there may be dysmenorrhea, premenstrual tension and an early or long lasting or stormy menopause.

Many patients are hypersensitive to drugs, or they react wrongly to some of them. Perhaps more often than the average for women they complain of dyspareunia or unsatisfactory sexual relations. Many submit fairly early in life to hysterectomy for myomas.

In many cases the discomforts complained of are not so much those of migraine as of the nervousness, hypersensitiveness, psychic instability and constitutional frailness that so commonly go with migraine.

Atypical Spells

In 1618 Charles Lepois made note of the fact that his spells were atypical; he had the nausea and vomiting but not the headache. Many migrainous persons have a scotoma without the headache or nausea; others have a unilateral prostrating headache without nausea or vomiting; others have curious attacks of abdominal pain, and others have only the days of depression and mental distress without headache.

According to Slight and Morrison in a series of 169 cases there were nausea and vomiting in 65 per cent, nausea alone in 14 per cent, and vomiting alone in 3 per cent. The headaches were unilateral in 66 per cent, limited to some small area in 26 per cent, and widespread over the head in 6 per cent.

presents in an individual are modified by the addition of another harmful inheritance Thus some allergists on finding sick headaches afflicting many of their patients jumped to the conclusion that migraine is simply a manifestation of allergy Actually the migrainous storm in the brain is like a mousetrap set off by a trigger Allergy is just one of the things that can spring the trap while a disease like hypertension is something that can set the trigger so fine that the trap can almost go off by itself

A Psychopathic Inheritance

Many persons with severe forms of migraine owe their misery to the effects of an added psychopathic inheritance an inheritance which produces inner conflicts unhappiness frustration needless worries and many difficulties in adjusting to contacts with the world There may be difficulty with compulsions inability to make decisions and conflicts between two parts of a split personality

Whenever a woman is having more than three bad headaches a week it is highly probable that she is either somewhat psychopathic or in some way is misusing her brain Either she is carrying burdens of work or responsibility too heavy for her or she is struggling with a life-problem she cannot solve or she is not getting enough rest or all through the night she is puzzling over questions she cannot or will not solve and put away

Mild Forms of Migraine Can Be Intensified

If one questions many bright intelligent patients one soon learns that many have or have had migraine in a form so mild or with attacks at such rare intervals that when they go to a physician they do not think to mention the trouble Others carry in latent form a tendency toward the disease They are like those many irritable epileptics who never have a fit Other migrainous persons appear to have inherited enough bad genes to get the typical temperament or the scintillating scotoma but not the headache or the nausea Now just let a woman with such a slight tendency toward migraine get some extra handicap or sensitizer such as a rising blood pressure or an allergy and soon severe and frequent headaches may be upon her Occasionally in older women an old tendency to migraine will flare up when the patient suffers one or more little apoplexies and slips into a mild state of agitated depression

Allergy

A high percentage of migrainous persons are allergic but their sensitivity to dusts pollens and foods probably is just a part of their exaggerated sensitivity

Thomas and Post (1925) believed that there is a relationship between the two diseases

Dizziness or Lightheadedness — It is probable that in many cases dizziness uncertainty in walking or fear of falling are due to the poorly balanced nervous system of a migrainous person Atkinson (1943) believed that Meniere s disease is related to migraine

Psychic Storms — Psychic migraine has been described by Liveing and others but it is impossible to say how much of the syndrome is due to migraine and how much to a separate psychopathic inheritance The writer thinks it best to describe migraine as it is usually encountered in hundreds of cases and to assume that the bizarre forms are mixtures of migraine and something else

Migraine a Continuation of Cyclic Vomiting in Childhood

Many migrainous patients can trace their headaches back to childhood, and many more if asked will remember that in childhood they were often sent home from school because of bilious vomiting ' Some will remember that the spells of vomiting came usually with any excitement such as an examination, a school picnic or a school play Some had short bouts of unexplained fever bad breath mental hebetude or diarrhea Anyone who has even seen a child with cyclic vomiting ' utterly dejected detached from his surroundings refusing to say a word apathetic and mentally not there will recognize the great similarity of his appearance to that of a patient in a severe attack of migraine

Rashford followed up a number of patients suffering from cyclic vomiting and found that many became migrainous, many were also allergic Hurst (1924) spoke of Osman s discovery that 23 of 52 patients with cyclic vomiting had a migrainous heredity

The Heredity of Migraine

Allan (1927) reported getting a history of migraine in the near relatives of 91 7 per cent of the migrainous persons he questioned Allan (1928) Buchanan (1920) and J C Smith (1922) concluded that the tendency is inherited as a Mendelian character probably dominant Miss Julia Bell (1933) who made perhaps the best study of the subject did not express an opinion as to the nature of the inheritance Allan believed that it is inherited equally by the two sexes but that the women have much more trouble with it than do the men

Conditions That Can Be Inherited with Migraine

Much of the literature on migraine is confusing apparently because the writers did not see that often the severity of the disease and the clinical picture it

INCIDENCE

It is impossible to state what percentage of the population or of a group of patients have migraine because (1) so many fail to mention it (2) so many have it in such a mild atypical form that it is hard to know whether to include their case in any enumeration and (3) the incidence varies so greatly with the intelligence and social status and occupation of the group studied

Migraine is a disease of the more intelligent upper fourth of the community In the course of many years the writer can remember seeing it in only two men who worked only with their hands He once saw it in a mechanic but when the man was asked what sort of work he did he said he was in charge of a large shop with many men under him

Buchanan (19 0) found migraine in 2 1 per cent of the records of 1 ,500 ad missions at the Mayo Clinic Crimes (1931) found it in 8 per cent of 15 000 cases studied in general practice Ball (1927) who questioned patients coming to an internist found migraine affecting members of 6 1 per cent of 7 000 families This is probably as good a figure as is available for the group of persons sufficiently intelligent and well to-do to consult a distinguished internist in a big city Fitz Hugh (1040) who reviewed 4 000 private office records, found a note about migraine in 22 per cent The disease afflicted 26 per cent of the women and 16 per cent of the men Elliot (1932) who questioned 5 000 patients consulting a distinguished oculist, found 6 per cent with migraine

Incidence at Different Ages

Although migraine commonly appears in childhood or youth and often tends to disappear as the patient grows older there are all sorts of variants The writer sees many men who by the age of 35 are about over their migraine and then occasionally he will see a man or woman of 65 having many severe attacks a month

Women are supposed to lose their headaches at the menopause but many do not and some who lose the headache go on having trouble with abdominal pain Some women state that their migraine began or became troublesome only after the menopause Many of these are a bit psychopathic or have troublous psychological problems

FACTORS THAT BRING ON AN ATTACK

Among exciting causes that bring on a spell patients mention getting tense or tired having to stand up for long traveling getting worried or angry over doing losing sleep enduring noise or excitement getting alarmed or frightened

to all stimuli That migraine is not just a manifestation of allergy should be obvious to anyone who has watched its victims go on with their sickliness and fatigue and headaches long after they have eliminated all offending foods from the diet Food constituted just one of the triggers that could start an attack, and after that was eliminated plenty were left, such as fatigue, excitement, worry and tension Ball (1927) found migraine associated with asthma in 23 per cent of his 1 000 cases with hay fever in 13 per cent , with urticaria in 28 per cent and with skin lesions in 10 per cent

Constitutional Inadequacy

Migraine is commonly made extra severe and disabling when the woman has inherited a frail and sickly body too weak to stand up properly to the strains of life Often she has defective and poorly functioning pelvic organs with dysmenorrhea and severe monthly storms

Epilepsy

A number of writers through the years have gathered statistics to show that a high percentage of persons with migraine have epileptic forebears Other students of the subject such as Allan (1927) Bassoe (1933) O Sullivan (1941) and H D Palmer (1945) could not find any more epilepsy among the migrainous than in other groups

The writer will not go into the controversy here partly because his own experience with more than 500 persons with migraine has not shown anything that looked like an abnormal incidence of epilepsy in the families and partly because he is impressed with the fact that epilepsy and migraine usually attack persons who are very different from each other in intelligence temperament and appearance

Also the drugs such as phenobarbital bromides and dilantin which can stop the coming of epileptic attacks usually have no effect in warding off attacks of migraine Evidently there are big differences between the two diseases and particularly, between the persons who suffer from them

Hypertension

Years ago Janeway noticed that migraine appears more often in persons with hypertension than in persons with normal pressure This may be due to a tendency of hypertension to transform a mild or latent migraine into a troublesome form of the disease In these cases treatment with potassium thiocyanate or splanchnicotomy may cause the headaches to come less frequently

evidence to suggest that migraine is accompanied by any change in the acid base equilibrium According to Diamond some patients have an increase in the amount of bile in the blood but many others do not

Beazell and Crandall (1935) measured the adenine nucleotide nitrogen the purine nitrogen and the uric acid in the blood and found no deviations from normal Others also found no abnormality in the amount of uric acid Apparently in migraine there is no abnormality of purine metabolism Palmer Scott and Elliott (1943) found no abnormality in blood guanidine The basal metabolic rate was normal in 51 patients studied by Moehlig (1931)

Riley Brickner and Kurzrok (1933) made hormonal studies daily for some time on the urine of 11 women and men suffering from migraine In the women the female sex hormone usually was absent or present in reduced quantities In 20 out of 29 instances a headache was preceded by the appearance in the urine of prolan the follicle stimulating hormone of the pituitary gland In 7 out of 9 of the migrainous women the injection of 2 c c of follutein brought on an attack of migraine Although an excess of prolan in the urine tended to be associated with an attack of migraine it did not always go with one There were many exceptions and puzzles Glass (1936) in one case found a decrease in estrin and an increase in prolan and was able to help the woman by giving estrin in oil and emmenin Theoretically the giving of estrin might restrain the production of prolan but it seldom does this well enough to relieve headache

Much in favor of the idea that in women migraine is often associated with some tide in the pituitary ovarian hormone function is the fact that in many cases pregnancy brings relief The pregnant woman has prolan but it appears to have a different origin and function from that of nonpregnant women Curiously in the same woman one pregnancy may bring relief and another not or relief will come only after the first few months In one case in which a woman with a severe frequently recurring migraine was well during pregnancy a bad headache came on the second day after delivery

Pathology

Little is known about pathological changes in the brains of persons with migraine because they do not die of the disease Changes have been found at necropsies but no one could say what relation they had to the migraine Some writers have tried to blame the pituitary gland for the symptoms but roentgenological studies of the sella turcica in several hundred patients with migraine showed nothing abnormal (Palmer 1945) The fact that in some persons the headache is always on one side such as the right suggests that in them the lesion is limited to one side of the brain

No cause for migraine is ever likely to be found in the abdomen The digestive

entertaining hurrying getting into a close room shopping, facing a wind, eating certain foods getting constipated, letting up on strain or work, lying abed late, exercising too much anticipating too eagerly facing bright lights or glare, enduring strong smells getting into a crowd worrying about work piled up ahead trying to do several things at once, doing things that are out of routine or failing to make a decision Among women menstruation or Mittelschmerz are common causes of trouble

Possible Changes in Body Chemistry before or during an Attack of Migraine — Naturally it has occurred to many students of migraine that those attacks which come at times when the patient has been quiet and rested and without obvious strain or mental turmoil must be based on some tide in the body s chemistry, and efforts have been made to find out what this tide is Unfortunately these studies have not revealed much of value

As Riley (1932) wrote as yet no thoroughly systematic study has been made of the body chemistry between attacks just before them and during them Because of the great difficulty and expense of such studies and the need for a large corps of workers to make many analyses simultaneously most investigators have studied only one little part of the body chemistry Riley, Soltz Brickner and Hare (1935) made a study of the urine blood spinal fluid and gastric contents without finding anything significant

In the urine Gerson (1930) and Goldzieher (1941) found a reduction in the elimination of chlorides before an attack In some cases Margolis (1929) found some pentose in the urine Franz (1907) made a fine study of a migrainous woman and found no abnormality at any time in the urinary acidity total nitrogen urea nitrogen creatinic nitrogen uric acid nitrogen ammonia nitrogen and undetermined nitrogen He studied also the various forms of sulfur without finding anything wrong According to Torta and Wolff (1943) urine collected during attacks of migraine headache contained some substance that caused the rectus abdominis muscle of the frog to contract to a much greater degree than did the material in specimens collected during the periods when there was no headache The chemical producing the contraction was not identified The 17 ketosteroid content of the urine increased during headaches

Pfeiffer Dresbach Roby and Glass (1943) found no consistent changes in the serum calcium potassium and phosphorus during headache The serum protein and hematocrit readings rose a little as one would expect them to in blood somewhat concentrated because of starvation and vomiting There may be some alkalosis before attacks (Myers Muntwyler Way and Danielson 1934)

Using Volhard and Fahr s excess water excretion test, Redisch and Pelzer (1943) found abnormalities during a headache in fourteen of fifteen migrainous patients According to some investigators the blood cholesterol remains within normal limits while others found it occasionally elevated There is not much

of itself becomes painful and adds a component to the headache After the first hour or two of aching the quality of the pain may change the throbbing may become less conspicuous and there may be a steady ache Sections taken from the temporal artery of patients after a prolonged attack of migraine were studied microscopically and the wall was found to be thickened This thickening can explain why ergotamine may not work if injected late in a headache the indurated wall can no longer contract

Some writers have thought that the attack of migraine might be due to an increase in intracranial pressure but Sicard (1913) von Storch and Merritt (1935) and Pool von Storch and Lennox (1936) found that during headaches the pressure of the spinal fluid varied little from normal and might be some 14 mm lower than in a control period Following an injection of ergotamine it rose 13 mm in the migrainous cases and 31 mm in the controls

Kerppola (1926) von Storch and Merritt (1935) and Riley Soltz Brickner and Hare (1935) examined the cerebrospinal fluid of migrainous patients and found no abnormality The pressure remained within limits of normal This fact will explain why a subtemporal decompression without tying of the middle meningeal artery does not cure migraine

The fact that in attacks of severe migraine there is such marked mental disturbance with utter misery and depression widespread paresthesias numbnesses weaknesses and perhaps dizziness together with the fact that the day before the attack there may be euphoria and excessive appetite suggests that in migraine much of the brain is affected

The fact that some patients never have another headache after a cerebral thrombosis suggests that some center necessary to the production of the migraine was destroyed Curiously a physician lost his migraine after a bad hemorrhage from an ulcer and many others have lost it for months after an attack of jaundice or the coming of disease in the liver Jaundice will for a time cure asthma and also severe arthritis as Hench and others have shown

Electroencephalographic changes have been looked for during attacks of migraine and not found Redisch and Pelzer (1943) found that during an attack of migraine the capillaries back of the nail and in the lips become contracted or blurred which suggests that in this disease the blood vessels are disturbed all over the body Hauptmann (1945) believed that the capillaries of most migrainous persons are always somewhat abnormal

Ophthalmic Migraine

This is probably a useless term that should be abandoned It has been given by some writers to the type of migraine in which the patient has a scintillating scotoma The name appears to have been given at times to that type of the disease

tract usually is perfectly normal so far as can be seen by the roentgenologist. Many physicians and laymen blame the liver but Morlock and the writer (1940) found that a large group of persons with severe disease of the liver were less subject to migraine than were the persons in a control group. The only reason why the migrainous vomit bile is that waves of reverse peristalsis begin in the jejunum and drive bile back into the stomach. There is no reason for suspecting that the bile is at fault.

Some few men have tried to blame migraine on duodenal stasis, but they apparently were confused by the fact that during a headache there can be stasis in the duodenum due to the storm coming down the vagus nerves. The writer has seen a number of patients who had undergone duodenojejunostomy, and none of them had been helped by it.

Mechanism of Migrainous Headache

Remembering how much the arteries in and about the cranium have to do with headache it will not be surprising to find that migraine also appears to be due mainly to relaxation and distention of some of the arteries on the surface of the brain. They dilate and then the blood goes pounding through them. Just let them be contracted by ergotamine or any other drug and the headache ceases.

As early as 1867 Mollendorf noted that migraine with the dilated blood vessels on the affected side resembles the condition that follows section of the cervical sympathetic nerves. Sometimes on glancing at a person in an attack of migraine one can see the dilated arteries or veins under the skin of the forehead and temple or rarely one can see that the face and ear are reddened. Gregory (18 9), Mollendorf (1867), Liveing (1873) and others noted that pressure of the finger on the dilated carotid or temporal arteries would for the time stop the headache. Confirmatory also of the arterial distention idea of the production of the migrainous headache is the fact that in man artificially produced distention of the temporal or some of the meningeal arteries will produce headache. A splendid study is that of Graham and Wolff (1938) who produced pain in man by suddenly injecting the temporal artery.

One would think that a rise in the pressure of the cerebrospinal fluid, which would dampen the pulsations of the vessels within the cranium, should diminish the severity of the headache in migraine but it does not do so. Actually in 6 subjects no reduction in the intensity of a migrainous headache was effected by raising the pressure of the cerebrospinal fluid from 700 to 1 000 mm of a physiological solution of sodium chloride (Schumacher and Wolff). Hypertensive headaches similarly were unaffected by raising the intracranial pressure.

According to Torda and Wolff (1945) headache arises often in distended branches of the external carotid arteries. Prolonged contraction of these arteries

makes the diagnosis of migraine with confidence just because he recognizes the apathetic and miserable appearance of the person in an attack or he recognizes a typically migrainous person who is getting episodes in a typically migrainous way after some strain worry excitement anticipation or fatiguing experience Now he is learning to recognize as migrainous bizarre attacks with which there is only occasionally an atypical headache

Migraine Complicating Organic Disease — There are occasions when it is well to recognize a migrainous personality because this can be confusing the picture of some other disease such as peptic ulcer The writer has seen cases of gallstones and ulcer in which all the nausea and vomiting proved on careful observation to be due to an associated migraine and best relieved by rest and ergotamine

A Helpful Family or Early History — In some cases one is helped by a history of a migrainous heredity cyclic vomiting in childhood freedom from attacks during pregnancies perhaps occasional days of mental haziness and detachment and depression and perhaps a history of a few attacks of typical migraine or scotomas years before Typical also is the story that a woman cannot give a dinner party without getting a sick spell

Several Types of Headache — One fact that often makes the diagnosis hard is that the patient has besides an occasional fairly typical migrainous headache many others which are hard to classify They may be ordinary headaches such as most headachy women have or they may be nuchal or fibrositic at times or they may be menstrual or due to hunger or delay in getting the morning coffee When as often happens the patient talks only about these common headaches the physician can easily miss the story of the more important ones

A Useful Test — *One way in which a patient can sometimes tell quickly* whether a given headache is going to be migrainous is to bend over as if to pick something off the floor or to lie down or while sitting to lower the head between the knees If this brings severe throbbing the headache probably is going to be a migrainous one In some cases this worsening of the throbbing when the patient lies down is so marked that the victim has to try to sleep sitting up

Atypical Cases — Even when the patient has had unilateral headaches they may have been so mild or so infrequent that it is hard to say if they were ever migrainous in nature Many persons also will have only one or two parts of the syndrome such as the dull hazy days or spells of nausea and prostration or the abdominal distress with or without the headache As has been said in some cases diagnosis is impossible unless one sees a patient in an attack and perhaps finds that it responds quickly to an injection of ergotamine Many a time the writer has not even suspected migraine until he saw the person in an attack and then all was clear

A Nasal Test — According to Richter (1935) several men have confirmed

in which the scotoma is an isolated phenomenon The writer's impression is that it is better not to coin a number of names for atypical forms of migraine, some probably represent migraine complicated by some other disease

Ophthalmoplegic Migraine

The term ophthalmoplegic migraine has been given to a rare disease or perhaps a collection of rare diseases in which a lesion affecting the brain stem, the oculomotor nerves or a visual tract, produces ocular paralyses or permanent defects in vision associated with attacks of perhaps co-existent migraine

Riley (1932 page 502) has summarized the reports of necropsies as they have appeared in the literature Lesions were found that explained the paralysis but no one could say that they had anything to do with the migraine The writer much doubts if ordinary migraine by itself ever leaves any permanent injury to vision or the external ocular muscles In 40 years he cannot remember having seen a case of this type Adie (1930) has described a number of interesting cases in which permanent hemianopsia eventually developed

Diagnosis

As von Storch (1941) once said so wisely one hour of careful questioning is worth ten hours of examining Actually aside from the evidence that one gets often from looking at the patient and especially from looking at him or her in an attack one rarely learns anything from a complete examination except that the results of all the tests are negative and the abdominal storm is probably functional in nature When one does find gallstones or a myomatous uterus that generally has little if any bearing on the problem of the migraine

When the history is typical and the headaches have been coming for years it hardly seems necessary or justifiable to put the patient to the expense of a complete neurological examination with roentgenological studies of the skull, an examination of the cerebrospinal fluid and an electroencephalographic study

The diagnosis of migraine often is very easy as when there is a typical unilateral sick headache with a preliminary scotoma and prompt relief with an injection of ergotamine (gynergen) Relief obtained with ergotamine probably is highly diagnostic In cases in which there is no scotoma no nausea or vomiting a bilateral headache or none at all and no good relief from ergotamine the diagnosis becomes difficult There are many cases in which the history is so vague and the attack so mild or atypical that a definite diagnosis is impossible

In the old days when the writer depended for his diagnosis on the characteristics of the headache complained of he was often in doubt and doubtless often wrong in saying that the spell was not migrainous in nature Today he often

slightest effort to cure her by avoiding certain habits perhaps of drinking gambling running after women overworking or just neglecting her which keep the wife unhappy

Those migrainous women who are fretting over an unhappy marriage must make up their minds what they are going to do about it If as often happens they can not make up their minds to get a divorce or a separation they must stop thinking about it and must try to make a better go of the marriage

Many migrainous women could be helped most by a good kindly psychiatrist who would go over their problems with them and help them to get better adjusted to life Unfortunately as yet there are not enough psychiatrists to go around and hence the internist or family physician must do the best he can The big thing he can do is to go short on examinations and long on interviews

As Wolff once wisely remarked one seldom needs to ask the migrainous woman about the queer psychic twists that would interest a Freudian usually she is sensible enough and her problems are the common and imple ones of the strains and dissatisfactions and frustrations and worries of ordinary life Only a few hours of simple psychoanalysis usually will be enough to lay bare her faults of temperament and living and her sources of mental trauma Perhaps even in an hour any wise physician with a good knowledge of the ways of the migrainous woman will be able to learn most of what he needs to know about her problems and the causes which in her case bring on the attacks or keep them coming Then he must try to help her to adjust better to life and to conquer her bad mental hab ts

Many migrainous persons leave the physician s office much helped when just shown what their disease really is and reassured in regard to brain tumor colitis cancer and the other diseases that they long have feared Once these fears have been allayed many will go home and put up with a good deal of suffering They will feel better about their disease also when they see that to a large extent the number of attacks they have in a year will depend on their own behavior Many a migrainous woman will struggle hard to get well because she knows that she is too irritable to be the good wife and mother she longs to be She knows that often when she punishes a child it is not so much because he was naughty as because she is so nervous and jumpy

Some women with executive ability who have been carrying heavy responsibilities outside of the home must retire for a time from the presidencies of societies and clubs and the chairmanships of committees Many a woman could *help herself greatly by resting in bed mornings for a few months and thereafter* taking a nap every afternoon In the case of many migrainous women a daily rest period or nap is almost essential to health Others must try to go to bed earlier and get more sleep In many cases it helps to keep a record of events preceding severe attacks a record which may reveal the things to avoid

the usefulness of Muck's (1924, page 1461) test for migraine in which one sprays with a 1:1,000 solution of epinephrine the nasal mucosa and on the side corresponding to the headache finds a white area instead of the normal red area found on the other side

Mixtures of Migraine and Histamine Headache

There are a few cases of what looks like migraine in which the patient can be thrown into an attack by an injection of histamine and can be helped by desensitization to histamine. Apparently there are mixtures of migraine and histamine headache.

Treatment

There are two main parts to the treatment of migraine: one consists of efforts to prevent the coming of the attacks or to lengthen the interval between them; the other is concerned with the problem of aborting or shortening or making less severe the attacks when they come.

Efforts to Prevent Attacks

From what has gone before it will be obvious that one must never expect to cure migraine so that it will never return. Usually the best and often the only way of making a woman less sensitive and therefore less subject to headaches is to have her get a good long rest, and this must be real rest. Naturally if she goes on a vacation and takes her troubles or worries or an unloved relative with her, she is not likely to get any benefit. Even if she leaves a disturbing husband at home, if she keeps worrying about him and what he is up to, she will return with her headaches as bad as ever. Some persons on a vacation will even play so hard that they will get no rest. A certain migrainous woman, told to give up her job and play golf, got a "pro" and worked so hard at the game that soon she was woman's champion of the club. No wonder her headaches kept coming. They stopped only when she stopped "playing" so hard. Often the best possible prescription for a migrainous woman would be one for a maid.

In cases in which the patient is employed, if the job is too exacting or nerve racking or if the conditions of work are unpleasant, relief can come only through changing occupation or employer. Oftentimes a woman is caught in a sort of trap at home or office, a trap from which she cannot escape, and then the prospects of successful treatment are rather hopeless.

In many cases the husband could be the best doctor if he would be kinder and more considerate, or if he could make the wife happy. Many a husband will spend large sums on medical treatment for his wife when he will not make the

sedative drugs such as bromides and phenobarbital should cut down on the frequency with which headaches come much as they cut down on the frequency with which seizures come in cases of epilepsy but actually in the writer s experience usually they have failed to help Similar poo results were reported by A O Dell after a follow up study Hurst said (1924) bromide has no effect in migraine in the least comparable to that which it has in epilepsy

The writer has little personal acquaintance with and not too much faith in many of the treatments that will next be mentioned but men have reported good results from using them Perhaps it is significant that in most cases the man who reported enthusiastically about the use of some drug never wrote a follow up paper and no one else ever wrote favorably or unfavorably about the method However many persons with migraine are desperate enough to try anything and hence most of the treatments recently advocated will here be mentioned.

Treatment with Hormones — If only because of the remarkable freedom from migrainous headaches that is experienced by many women during pregnancy it would seem that every effort should be made to find a hormone that will give a similar measure of freedom Unfortunately the requisite one has not yet been found Today most women with severe migraine are treated with ovarian hormones but usually the results are nil It would seem that more research should be done with the hormones that are abundant during pregnancy

As already noted Riley Brickner and Kurzrok (1933) and glass (1936) found that usually in migrainous women there are subnormal amounts of estrin and excess amounts of prolan By injecting follutein or prolan usually they could throw a migrainous woman into an attack Brock O Sullivan and Young (1934) did this also with large doses of ammiotin These results suggest that these substances should not be used with the idea of preventing migraine

Moffat (1937) once advised the giving of increasing amounts of follutein during the two weeks preceding menstruation but the few experiences the writer had with this treatment were unsatisfactory the results being nil Brock O Sullivan and Young (1934) did not get any results with ovarian follicular hormone but A P Thompson (193) reported some Leyton (1943 and 1944) used on both men and women antuitrin S or the anterior pituitary like hormone obtained from pregnancy urine He claimed good results in 60 per cent of cases but advised against the use of the substance for more than three months at a time for fear of producing an antihormone He began with 25 units and used as much as 500 units of it Some persons are sensitive to the drug and may react with nausea or an attack of migraine He tried estrin and progesterone without much result Von Storch (1941) gave antuitrin in doses of 100 to 200 rat units three times a week Thomas R Brown (19 9) and Stevens tried pituitary extract but gave it up Soltz Brickner Riley and Salmon (1935) reported some good results from giving to women 5 c c of amniotin by mouth divided into three doses The

Food Sensitiveness — If headaches are coming several times a week, the patient should go on an elimination diet to see if this makes any difference Such a diet may consist of nothing but let us say beef and lamb, broiled or roasted or boiled (without the addition of any condiments and eaten without gravy) with in addition rice oatmeal potato, carrots, asparagus, string beans, a little butter, sugar canned pears, apple sauce (unseasoned) or lemon gelatine These foods have all been chosen because they seldom give trouble allergically Naturally, if the patient already knows that any one of these foods causes headache she should avoid eating it Such a diet can be kept up for a week or two until the patient can tell whether or not it is helping While on this diet the patient should take no drink besides water and no candy laxative gum or anything else

Combining the lists of commonest offending foods published by Hinshaw and the writer (1935) Vaughan (1939) Cowin (1932) Elliot (1935) and Sheldon and Randall (1935) one finds prominently mentioned chocolate, onion milk, cabbage eggs peanuts coffee and meat

If on the elimination diet the headaches should stop coming then the patient should begin immediately with the testing, one after the other of the foods that are commonly eaten These foods should be tested repeatedly until they can be classified as good or bad Each food may have to be tested for three or four days in succession because occasionally foods that can be eaten safely for one day cannot be eaten for several days running without bringing an attack

If a patient s headaches are coming only at intervals of weeks or a month or two then the offending food granting that there is one can better be identified by keeping a record of the unusual foods eaten just before each headache comes After several episodes the record may show that before each attack one certain food always had been eaten If so this should be left alone for a while to see if the headaches disappear If they should keep coming it will be obvious that this food was either not at fault or else was not the sole offender

The skin tests for foods are usually not reliable but occasionally they will give some help

Avoiding Constipation — In a few cases the patient can be relieved of head aches by the avoidance of constipation perhaps by taking each night or morning an enema consisting of one or two quarts of warm water with a rounded table spoonful of sodium chloride Hurst (1924) said his experience showed the folly of attempting to treat migraine with aperients and freak diets designed to avoid toxemias

Protection against Light and Sound — A great help to a migrainous woman is an eyeshade made of cloth which can be put on for a nap or for sleeping after four o clock of a summer morning Good ear plugs when they become available will also be a tremendous help

Drugs with Which to Avoid Headaches — Theoretically in cases of migraine

interval between attacks of migraine Drewyer (1940) also reported good results with it The experience of the writer with this drug has been disappointing

Some physicians have tried to prevent the attacks of migraine by giving ergotamine tartrate every day Theoretically it is hard to see why this should work and certainly it would appear to be dangerous to keep a person in a constant state of ergotism with contracted blood vessels What perhaps saves many from getting into trouble is the fact that the daily dose of ergotamine is taken by mouth and the person absorbs but little of it Bellergal sometimes used in this way is a mixture of ergotamine, phenobarbital and belladonna Its use is not very logical

Because of the fact that many persons lose their migrainous attacks for some time after they have had jaundice one of the most hopeful lines of attack on the problem would be to search for some substance that would safely produce temporary jaundice According to James (1945) 0 00 gm of carbachol (carbaminoyl choline chloride) can be helpful A tablet was given three times a day by mouth but twice the amount could be taken

Pelner and Aibel (1942) gave by mouth increasing doses of prostigmine bromide and reported hopeful results They took a 15 mgm tablet dissolved it in 30 c c of water and on the first day gave one two and three drops morning noon and night respectively They increased one drop with each dose until thirty drops were being given Following this thirty drops were given each day for a week and then three times a week for an indefinite period Shay found that this sometimes works well

In 1941 H D Palmer reported good results from treatment with vitamin B_1 but in many of the writer s cases the patients had tried it without result In 1945 Palmer advised the giving of large doses of B complex with niacin and pyrodoxine Pfeiffer and associates (1944) reported excellent results from the use of a mixture of calcium lactate and potassium chloride They prescribed a mixture of calcium lactate 30 8 gm and potassium chloride 22 5 gm dispensed in capsules Enough of these were taken each day to give a total dose of 0 65 gm No effort was made to restrict the use of sodium chloride in the diet At the first sign of a headache the patient took 1 3 gm and if necessary repeated the dose an hour later

Hopeful is the report of J A Brown (London Lancet 1943) who found accidentally that the giving to his patients of 1 3 gm of urea a day would stop the coming of migrainous or other types of headache Benadryl is now being tried out but so far with disappointing results in many cases Barborka (1930) tried the ketogenic diet but the method has not taken hold. Schnabel reported poor results with it Goldzieher (1946) reported good results from giving a high protein low carbohydrate diet with restriction of fluids and sodium chloride MacNeal and Alpers (1947) advise the use of octin (Bilhuber) by mouth or hypodermically as a preventive and also as a reliever of headaches

5 c c contained 2 000 rat units The amniotin was prepared by Squibb and Sons

Dunn (1941) injected progynon or estradiol benzoate in doses of from 2 000 to 10 000 rat units He said this aborted attacks and lengthened intervals Sajitz also used progynon Particularly in the case of menstrual migraine Blakie and Hossack (1932), Whitehead and McNeil (1935), von Storch (1941) and Glass (1936) have given emmenin in doses of from two to three teaspoonfuls (8 to 12 c c) by mouth daily during the week before menstruation Excellent results have been reported Emmenin is an ovary stimulating hormone derived by Collip from the placenta

Treatment with Thiocyanate — Hines and Laton (1942 1943) while treating hypertensive headaches with potassium thiocyanate discovered that in some cases of migraine the drug cut down the frequency of the attacks They advised maintaining the thiocyanate level in the blood at from 10 to 12 mgm per 100 c c Symptoms of intoxication such as nervousness drowsiness dermatitis nausea and vomiting must be watched for Bassoe (1933) reported an occasional good result from injecting intravenously 1 gm of sodium thiocyanate just as an attack was starting Ingle and Evanson (1942) advised giving 0 39 (gr 6) at the beginning of an attack

Treatment with Many Other Drugs — The favorite drug in the old days was cannabis indica given in the largest dose the patient would tolerate Some began with 54 mgm (gr $\frac{1}{15}$) of the dried extract three or four times a day and ran it up to 15 mgm (gr $\frac{1}{4}$) every four hours Bassoe tried it repeatedly but without much success Occasionally iodides or thyroid substance will appear to help Some patients appear to be helped by the cutting down of the water intake They say they then have less nausea in the attacks

In 1923 Joseph L Miller and C O Raulston reported good results from intravenous injections of a 5 per cent solution of peptone (Armour) They began with 0 5 c c and quickly ran the dose up to 2 c c They usually gave two injections a week If they saw no results after eight or ten injections they stopped When the treatment helped the results were temporary In 1927 F E Ball reported good results in 35 per cent of cases but Thomas R Brown (1929) was not so optimistic Rowe (1931) used it subcutaneously for only three weeks at a time The writer had good results in one case and then many failures

Because Hare noted that migrainous persons who contracted typhoid fever were for a time cured of their headaches some physicians have injected typhoid vaccine in doses sufficient to raise the patient s temperature to about 103° F (39 4° C) The initial dose was around 20 000 000 organisms Sometimes six or eight injections were given

In 1936 Crandall Roberts and Snorf found chondroitin sulfuric acid (Wilson) in doses of from 2 to 4 gm (gr 30 to 60) a day would sometimes lengthen the

artery it is said that the attack can be stopped usually by the injection of a solution of procaine hydrochloride around the vessel If this result is secured several times in succession then the artery can be ligated with considerable hope that a cure will be effected at least for a while Patzer (1945) reported work along these lines and Nadler (1945) had excellent results from infiltrating the temporal arteries with 2 c c of a 1 per cent solution of procaine hydrochloride and later sectioning them Nadler s 8 patients were doing well when he reported on this treatment

Operations on the Abdominal Organs — Most women with severe migraine have at some time parted with the appendix others with the gallbladder and many with the uterus but in the experience of the writer such operations almost always fail to bring permanent relief

Bassoe (1933) Moehlig (1931) and Buchanan (1924) commented on the high percentage of migrainous women who have had futile operations operations which would never have been performed if the surgeon had either known that the patient s disease was migraine or that migraine cannot be cured by operations on the digestive tract

Moehlig s 69 women patients had had 32 laparotomies and in Buchanan s group 75 per cent had had futile operations Duodenojejunostomy has not worked well and is now generally abandoned

Production of an Artificial Menopause — Because some women lose their migraine at the change of life a few physicians have tried to cure the disease by bringing on an artificial menopause either by means of hysterectomy or by the use of radiation This is not advisable because in a series of more than 50 cases studied by the writer only 1 woman in 7 was relieved and 1 in 3 was made much worse

Naturally the highly sensitive and nervous type of migrainous woman is likely to have a stormy time after the loss of her ovaries The statements in the older literature to the effect that in women migraine stops at the menopause are wrong one often sees severe migraine in women past fifty Some women even begin to have their troubles with migraine after the change of life

Correction of Refractive Errors and Muscular Imbalances — Many men have claimed to cure migraine by fitting glasses with the greatest of care and the writer has seen a few cases in which great relief was given a patient by a good oculist

Elliot (1935) an oculist who studied the subject at length and was very enthusiastic about his cures is the more convincing because he claimed good results in only a fraction of the cases It is convincing also that Hurst (1924) who sent him many patients reported cures in the cases of some Doubtless all persons with migraine should have at least one thorough study by an able oculist with a check not only of refractive errors but of muscular imbalances

Perhaps influenced by the improbable idea that the liver has something to do with migraine G C Hunt (1933) in England gave sodium glycocholate in dosages varying from 0 13 to 1 3 gm (gr 2 to 20) three times a day He reported good results but the method has not been taken up in the United States Decholin would be a more promising drug to try, and some physicians have given it

Resection of Nerves and Arteries — Love and Adson (1936) reviewed some of the literature on the results of cutting the sympathetic nerves in the neck and reported a study of 18 patients who had had severe headache and who had had the cervical sympathetic nerves resected for the relief of arterial spasm in an arm Of the 16 patients from whom replies were obtained later 12, who had had migraine said that they were either partially or completely relieved of the headache and 4 were not helped 3 were completely relieved Eight of the 12 patients who obtained relief, had been operated on for Raynaud s disease It may be significant that in the 4 cases in which there was no improvement the patient did not have a typical migraine Love and Adson did not feel happy enough about their end results to go on operating for migraine Dandy reported good results from cervical sympathectomy in - cases of what appear from the descriptions to have been histamine headache rather than migraine Probably significant is the fact that he did not continue to report on the use of this operation in similar cases

Rowbotham (1942) in 2 cases of migraine sectioned parts of the trigeminal nerve with good results In another case he divided the supra orbital and supra trochlear nerves and brought relief He said that White (1942) and Telford had questioned the wisdom of doing a sympathectomy for migraine Dickerson (1933) in 7 cases of migrainous or traumatic headaches ligated the middle meningeal artery with striking relief of headache on the side operated on Some of the patients relapsed after a few months Sutherland and Wolff (1940) had the middle meningeal artery tied in the treatment of persons who were improved thereby for a while Nadler (1945) had the temporal arteries ligated and sectioned in 8 cases and reported that headaches were still absent from 2 to 11 months later

In a case of severe migraine with the pain always on the left side the writer had some of the cervical sympathetic ganglions on the affected side removed The headaches stopped but the patient got such constant and terrible pain in the left arm that her life became unbearable and she became addicted to morphine A number of similar unexplained misfortunes with nerve sections caused the writer to give up efforts along this line of therapy The fact that the surgeons who reported a few operations on patients with migraine did not go on reporting more cases suggests that they too ran into poor end results In one case of the writer a subtemporal decompression did not relieve the headaches

Injection of Procaine Hydrochloride about the Temporal Artery — When headaches occur only on one side of the head with marked throbbing of the temporal

nausea and retching If a suppository is not available two or three capsules of some barbiturate can either be pushed into the rectum or their contents can be suspended in a little water and injected with a small syringe

Rest and Isolation are Helpful — In any treatment of migraine it is helpful to have the patient lie down for a while in a darkened room Migrainous men commonly are able to force themselves to stay at work but their sisters with the disease often find this impossible

Many years ago Tissot remarked so wisely that During the paroxysm there is scarcely anything to be done the patients are so afraid of noise motion or anything approaching them that they infinitely prefer to be left perfectly quiet than to be tormented with useless measures

The Treatment of Mild Attacks — In mild attacks in which the nature of the headache is doubtful acetylsalicylic acid acetanilid acetphenetidin antipyrine aminopyrine or sodium salicylate will raise the threshold for pain and perhaps will block the storm especially if given quickly as soon as the ache starts

According to those who have measured the influence of these drugs on the threshold for pain acetylsalicylic acid is the best of the lot and it does *not help* to combine it with another drug of the same type or with codeine or a barbiturate or some bromide If codeine is used at all it should be used in a dosage of from 0 032 to 0 065 gm (gr ½ to 1) Measurements have shown also that it does not help to take more than one 0 3 gm (gr 5) tablet of acetylsalicylic acid at a time the threshold for pain only comes up against a ceiling beyond which it cannot go unless one shifts to some derivative of opium Since the effect of one dose of acetylsalicylic acid begins to fade in about an hour and a half it is well to take a tablet every two hours in order to maintain the effect Aminopyrine should be *used with caution because of its highly toxic effects on some few persons*

In spite of the evidence supplied by the measurements of pain thresholds many physicians doubtless will continue to use combinations of analgesics some of them with proprietary names A score of times at the request of a patient the writer has looked up the composition of some supposedly miraculous remedy for migraine only to find that it was the usual mixture of acetylsalicylic acid acetphenetidin and caffeine

A favorite combination much promulgated years ago by Fantus is an old prescription of Lauder Brunton It can be written as follows

Rx Sodium salicylate	6 gm
Potassium bromide	12
Sodium bicarbonate	12
Mix and divide into six blue powder papers	
Tartaric acid	10
Divide into six white powder papers	

LABEL Mix contents of a white and blue paper each dissolved in half a glass of water Repeat the dose hourly if necessary

Treatment of an Attack

The first principle in treating an attack of migraine is to begin the minute the first signs of trouble appear The longer a headache has been under way, the harder it is likely to be to stop it with any medicine Recently it has been shown that, after a headache has lasted some time the wall of the affected artery becomes thickened so that it will no longer contract well under the influence of ergotamine It has been shown also that after a headache has lasted for some time, sedative drugs cannot raise the threshold for pain as they did before

However often the patient so hates to stop and take medicine, or she is so afraid of it or her relatives are so critical of her taking it that she waits until she becomes so hypersensitive or worn out or demoralized that no drug can then help much Oftentimes if the patient would only take a tablet of acetylsalicylic acid the minute she feels a headache starting she could get relief, or if, when she feels herself getting tense and jittery she would promptly take one or two tablets or bromural or other sedative and would lie down she might abort the impending attack

As has been pointed out in the section on diagnosis, a great difficulty of migrainous women is that they often have two or three types of headache As a result when they begin to feel bad they do not know which type of ache is on its way, they hope that it is going to be only a mild one and so they wait and do nothing later when they discover that what has come is a bad attack of migraine it is late for successful treatment or at least for the taking of any drug by mouth As I have noted oftentimes one can recognize a migrainous spell by reaching down as if to pick something off the floor if this starts the head to pounding and throbbing serious trouble is on the way According to Muck (1926) hyperventilation for two minutes will bring on a typical attack, especially if it is impending

Medicine is Useless When Taken by Mouth — One of the most important points that a migrainous person and every physician must remember is that once great distress with nausea and perhaps vomiting have come the taking of any medicine by mouth is likely to be useless because even if it were to stay down it would not be passed on into the bowel and be absorbed In an attack of migraine the stomach often does not empty well, and as physiologists know absorption from the gastric mucosa is limited and uncertain Hence it is that once an attack of migraine is well under way all medicines should be injected either under the skin or into the muscles or veins or into the rectum

Some patients get great help from the commercially available rectal suppository containing 3 grains (0 2 gm) of pentobarbital sodium (nembutal) If the patient inserts one or perhaps even half of one of these suppositories in the rectum and lies down in a darkened room he or she may sleep for a few hours and wake up well The drug may quiet the vomiting center and put a stop to

CHAPTER XXVII

SYDENHAM'S CHOREA

By ROBERT F. WATSON

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INTRODUCTION

Synonyms.—Chorea minor, St. Vitus' dance, juvenile chorea, rheumatic chorea, *encephalitis rheumatica*, chorea Sancti Viti, Veitstanz.

Historical.— (χορεία = dancing). The term St. Vitus' dance employed by Sydenham[1] for the name of the symptom complex first

From about the middle of the nineteenth century until appearance of the work by Gerstley and his coworkers[10] in 1935 chorea was generally accepted without question as a manifestation of rheumatic fever Although this concept is still maintained by most authorities a number of articles have appeared during the past ten to fifteen years emphasizing the possible importance of the emotional aspects and pointing out that all chorea may not be rheumatic in origin

Definition — Sydenham's chorea is an acute nervous disorder of unknown etiology which occurs predominantly in children frequently in association with other rheumatic manifestations and is characterized by involuntary quick jerky purposeless movements of the extremities facial grimacing emotional instability and muscular weakness It is generally believed to be a manifestation of rheumatic fever and therefore cannot be considered a distinct disease entity

Incidence

There are no accurate figures on the incidence of chorea as it is not a reportable condition Only in Norway Denmark and Iceland is rheumatic fever reportable and in these countries chorea is regarded as a manifestation of that disease One means of estimating the incidence of chorea in this country is from reports of the admission rates to hospitals From a survey of 36 civilian hospitals in Philadelphia Hedley[11] found that patients with chorea accounted for 0 09 per cent of all admissions and approximately 0 37 per cent of all medical admissions In a similar survey of hospitals in Cincinnati Wedum and Wedum[1] found that 0 59 per cent of all admissions were for chorea patients These figures would be multiplied several times for children's hospitals

Paul[12] in 1930 estimated there were 840 000 cases of rheumatic heart disease in this country with a population of 100 000 000 people On the basis of these figures there would be 1 100 000 persons afflicted with rheumatic heart disease for a population of 140 000 000 Since approximately 15 per cent of patients with rheumatic heart disease have had chorea[13] there would be at least 165 000 persons in this country who have suffered from this disorder

The incidence of rheumatic fever and probably also chorea are on the decline in this country as well as in Great Britain Statistics from the Metropolitan Life Insurance Company[14] showed the death rate of policy holders between the ages of five and twenty four years from

described by him in 1686 and since commonly known as Sydenham's chorea had its medical origin in the dancing manias of the fourteenth, fifteenth and sixteenth centuries During this time under the influence of religious excitement outbreaks of hysteria, dancing mania, occurred in Germany and the Netherlands The sufferers in search of relief made pilgrimages to various shrines including that of St Vitus at Zabern, which was especially famous St Vitus a Sicilian, whose body was removed to France was the patron saint of actors and dancers and his altar was the haunt for all kinds of intercessions including that of relief from the dancing mania According to Hecker, Paracelsus at the beginning of the sixteenth century made a special study of dancing mania and gave to it the name chorea Hence the term chorea sancti viti arose to describe the dancing mania a form of hysteria It is unfortunate, as Osler[3] pointed out that Sydenham used the *name* St Vitus' dance for a condition that has nothing to do with chorea sancti viti

Sydenham's Schedula Monitoria[1] contains the first accurate description of the symptom complex chorea minor, as we know it today His description of the affection in the Schedula Monitoria is as follows 'This disorder is a kind of convulsion which chiefly attacks children of both sexes from ten to fourteen years of age It first shows itself by a certain lameness or rather unsteadiness of one leg, which the patient draws after him like an idiot and afterwards affects the hand of the same side which being brought to the breast or any other part cannot be held in the position a moment but is distorted and snatched by a kind of convulsion into a different position and place notwithstanding all his efforts to the contrary If a glass of liquor be put into his hand to drink he uses a thousand gestures before he can get it to his mouth, for not being able to carry it in a straight line thereto because his hand is drawn different ways by the convulsion as soon as it has happily reached his lips he throws it suddenly into his mouth and drinks it very hastily as if he only meant to divert the spectators'

Bouteille[4] was the first to call attention to the close association that exists between chorea and the rheumatic state Richard Bright gave an excellent description[5] of the condition and also called attention to the association of pericarditis with chorea[6] Todd[7] taught of the close relationship of chorea and the rheumatic diathesis However, it was See[8] and Roger[9] who established the close relationship between chorea and rheumatic fever Roger maintained, as most workers do today, that chorea polyarthritis and endocarditis are different manifestations of the same disease

the report of the Collective Investigation Committee of the British Medical Association by MacKenzie it was found that some other member of the family had had chorea in 63 (14 per cent) of the 439 cases of chorea investigated while there was a history of rheumatic fever in another member of the family in 199 (45 per cent) of the cases. In a study of 554 cases of chorea Osler[3] found there was a history of previous attacks of chorea in other members of the family in 80 (14 per cent) of the cases. That the familial incidence of rheumatic fever is high is a generally accepted fact. Most recent reports on the familial incidence of rheumatic fever include chorea as a manifestation of that disease and do not give separate data for chorea. The high familial incidence of rheumatic fever, of which chorea is probably one manifestation, could be explained theoretically in one of three ways: (1) as an inherited susceptibility to rheumatic fever, (2) as due to certain common environmental conditions which favor the disease affecting the members of one family, or (3) as due to direct contagion. Wilson's work suggests that the familial tendency is due to an inherited susceptibility transmitted as a single autosomal recessive gene. Others believe that the high familial incidence is more likely due to common environmental factors, contagion or both. It is possible that all three factors play a part and the relative importance of any one is still uncertain and may not be determined until the etiology of the disease is known.

Age.—In his original description of chorea Sydenham[1] stated that it chiefly attacks children. The fact that chorea is rather sharply limited to childhood and early adolescence is now well recognized. From a series of 1 573 cases collected from the literature by the present author it was found that only 39 (2.5 per cent) occurred in children under 6 years of age, 677 (43 per cent) occurred in children 6 to 11 years, 695 (44.2 per cent) from 11 to 16 years, 128 (7.8 per cent) from 16 to 21 years and only 40 (2.5 per cent) in persons above the age of 20 years. From these figures it is apparent that 87.2 per cent of the cases occurred between the ages of 5 and 16 years. It is very uncommon before the age of 3, although Poynton has described chorea in a baby of 10 months. After the age of 15 the condition occurs predominantly in females and after the age of 18 usually in association with pregnancy (chorea gravidarum). The occurrence of Sydenham's chorea is uncommon in the male older than 16 years and in the female more than 20 years of age unless it is associated with pregnancy. It is the opinion of the present author that many of the cases described in the literature as occurring in older adults are not true Sydenham's chorea but probably represent

rheumatic fever and chronic heart disease (90 per cent rheumatic) had declined from 32.3 per 100,000 in 1917-18 to 9.7 per 100,000 in 1943. In Great Britain Glover[15] found the crude death rate for rheumatic fever had decreased from 67 per million in 1901 to 12.1 per million in 1942. Not only has the incidence of chorea probably decreased, but it also has apparently diminished in severity.

ETIOLOGY

The exact cause of chorea is unknown. Most workers regard chorea as a manifestation of rheumatic fever, the etiology of which also is unknown. Although a discussion of the causative agent, if there be one, or the mechanism by which it is induced, cannot be given, certain facts regarding the occurrence of chorea are known, some which may be of etiological importance and will now be considered.

Geographical Incidence. —Although we have no accurate information on the occurrence of chorea in many parts of the world, it most commonly occurs in the colder parts of the temperate zones and has, in general, the same geographic distribution as rheumatic fever. Like this disease, chorea is common in the northern half of the United States, Canada, the British Isles, the northern part of Europe and the southern part of Australia. It appears to be much less common in our own southern states, the southern part of Europe and in those countries which have tropical or semi-tropical climates.

Seasonal Incidence. —Chorea has a definite seasonal trend which also parallels that of rheumatic fever. In the United States and most of continental Europe the incidence rises gradually during the winter, reaches its peak in the spring during the months of March, April and May and then decreases gradually during the summer to reach a low point in the early fall.[16, 17, 18] In the British Isles, on the other hand, the peak incidence of both rheumatic fever and chorea occurs in the late fall and early winter months.[19, 20, 21] The reason for this difference between the seasonal incidence in the United States and England is not clear, but in both countries the curve parallels that for upper respiratory tract infections.

Race. —All races appear to be susceptible to chorea, however, the condition occurs less commonly in the Negro and American Indian in this country than in the white race.[3, 3, 24, 11, 12]

Familial Tendency. —A history of previous attacks of chorea or rheumatic fever in other members of the family is not uncommon. In

was first noted following fright or some other type of psychic trauma On close questioning however it is frequently very difficult to relate the onset of the chorea to the incident which was often very trifling It appears more likely that in most instances the child already suffered from chorea which was made more manifest and perhaps was recognized by the parent for the first time following some emotional upset Also it is natural for the mother to try to relate the onset of nervousness in her child to some recent incident which she believes may have been causative This trait of attempting to relate the onset of illness to some accident or recent event often of no etiological significance is common to a large percentage of patients especially those belonging to the class affected by chorea

Recently some doubt concerning the relationship of all chorea minor to rheumatic fever has been expressed by a number of workers These authors point out that an appreciable number (o per cent to 30 per cent) of chorea patients exhibit no other clinical or laboratory evidence of rheumatic fever and suggest that psychogenic factors may be of particular importance etiologically in this group of cases

Gerstley and his associates[10] stated that chorea may be caused by rheumatic fever but this is only one of many immediate causes and that psychic trauma seems far more important They also hold that chorea should not be taken as an indication of rheumatic fever without other rheumatic manifestations Coburn and Moore[21] report that in their experience one half of all cases of chorea occur in non rheumatic subjects and that chorea per se does not suffice for the recognition of rheumatic subjects nor for the diagnosis of rheumatic activity Hubble[7] regards chorea as a functional disorder of the nervous system often induced by acute psychic trauma or prolonged psychic stress Kagan and Mirman[22] conclude that chorea associated with an increased sedimentation rate is in most instances a manifestation of active rheumatic fever but that those patients who have their first attack of chorea with a normal sedimentation rate in the absence of congestive heart failure do not have rheumatic fever and are no more subject to its sequelae than are other normal persons They suggest that psychogenic factors may be particularly important in this group

In this regard it should be pointed out that for many years various writers have claimed that chorea affects predominantly children who normally tend to be introverted serious minded active high strung and more intelligent than the average These workers believe it is uncommon to see chorea affect the placid easy going extroverted child who is

other types of neurological disorders with associated choreiform movements Although rheumatic fever exclusive of chorea is most common between the ages of 5 and 16 years it is commonly seen in young adults of both sexes and is not rare above the age of 40 years

Sex – The greater frequency with which chorea occurs in girls has been commented upon by many investigators, in most studies the proportion has varied between 2 and 3 to 1 Of 3,982 cases collected by the present author from the literature 2,738 (68.8 per cent) were females and 1,244 (31.2 per cent) were male a proportion of slightly better than 2 to 1 The possibility that some endocrine factor plays a role in the production of chorea is suggested not only by its predominance in girls but that it rarely occurs in males after puberty and in older females it is usually associated with pregnancy (chorea gravidarum) When chorea is excluded as a manifestation, rheumatic fever occurs with about equal frequency in the two sexes

Social Conditions – Chorea, like rheumatic fever, affects chiefly children of the poorer class it is relatively uncommon to see chorea in children of the well to-do[5, 16, 8, 11, 30] In the report of the Collective Investigation Committee of the British Medical Association by Mackenzie only 12 (8 per cent) cases of 430 reported were from the upper class Still[9], in the report by the Medical Research Council states that in a private practice dealing almost exclusively with the well to do there were amongst 700 consecutive cases between the ages of 6 and 10 years only 5 (0.7 per cent) cases of rheumatism including one of chorea, while in the out-patient department at King's College Hospital amongst 229 cases of the same age group 13.1 per cent had acute rheumatism 3.5 per cent with joints and the rest with heart affections or chorea Hedley[11] in this country found that only 19 (2.5 per cent) of 765 cases of chorea were admitted to the private or semi-private wards of 36 general civilian hospitals in Philadelphia while a few years earlier it had been estimated that 35 per cent of all patients admitted to general hospitals occupied private or semi private rooms The fact that chorea and rheumatic fever occur with much greater frequency in children of the poorer class suggests that contagion or some environmental condition common to this class of people or both is of etiological importance

Emotional Factors – Psychic trauma, such as fright grief shock overwork at school and excitement of various types has long been considered important in precipitating attacks of chorea In some studies the incidence of such precipitating factors has been very high, while in others it is equally low It is often stated by the parent that the chorea

to show any other evidence of rheumatic fever while the remaining 184 (58 per cent) subsequently developed other rheumatic manifestations In another 164 patients chorea occurred subsequent to the onset of their rheumatic fever In other words of 48 patients who suffered chorea 134 (8 per cent) exhibited no other evidence of rheumatic fever, whereas the remaining 348 (7 per cent) had other rheumatic manifestations either before or following the chorea attack These figures are not out of line with those reported by other workers Wilson Lingg and Croxford[13] found that 42 per cent of their rheumatic children had chorea Coombs[36] reported that on careful analysis of 27 cases of chorea 76 per cent had other manifestations of rheumatic fever Of 416 young rheumatic subjects studied by Ash[30] 34 4 per cent developed chorea and of 138 chorea patients 7 per cent at some time showed other evidence of rheumatic fever

It is well known that an appreciable number of all attacks of chorea (15 to 0 per cent) either precede or follow immediately a bout of rheumatic fever the manifestations of one condition gradually subsiding while those of the other make their appearance In such cases it is more common for the chorea to follow on the heels of the rheumatic episode It is not unusual however to find evidence of active rheumatic fever during the attack of chorea In about 0 to 30 per cent of cases no other manifestations of rheumatic fever appear, in the remaining 50 to 6 per cent the rheumatic fever either precedes or follows the chorea by a number of months or years

The incidence of heart disease in chorea and rheumatic fever as reported by various workers is shown in Table I It is clear from this Table that about 45 per cent of all cases of chorea develop heart disease which is indistinguishable clinically and pathologically from that found in rheumatic fever It is also apparent that the incidence of heart disease in cases of so called pure chorea is appreciably less than in those who also had other manifestations of rheumatic fever the incidence of heart disease in the latter group approximating that for cases of rheumatic fever alone These data indicate that the patient with pure chorea has a good chance of escaping valvular heart disease while the appearance of other manifestations of rheumatic fever very definitely increases the risk of permanent valve damage to the heart

From the preceding discussion it is apparent that chorea and rheumatic fever are very closely associated It is still not possible to say with finality that all chorea is a rheumatic manifestation However it is impossible at present to differentiate the non rheumatic chorea from the

rather dull intellectually Others do not agree with this concept and hold that the dull may be affected as frequently as the more sensitive and intelligent child

Relationship of Chorea to Rheumatic Fever — There was little doubt in the minds of most of the earlier workers[5, 3, 4, 34, 35, 36] that chorea was a manifestation of rheumatic fever, and most recent workers[3, 38, 39, 40, 41, 11, 7, 4, 43, 41] continue to regard it as such The observations upon which this concept is based will now be discussed

It has been previously pointed out that the geographical and seasonal incidence of chorea and rheumatic fever parallel one another It has also been shown that both conditions affect predominantly persons of the poorer class and that chorea families have a high incidence of rheumatic fever Although these facts do not definitely relate chorea to rheumatic fever, they are in accord with such a possibility The more important data relating chorea to rheumatic fever come from many careful pathological and clinical observations Sixty two of the 73 fatal cases of chorea collected from the literature by Osler[3] showed endocarditis, which was also present in 4 of his own 5 cases In discussing the condition of the heart in chorea, Osler stated "*There is no known disease in which endocarditis is so constantly found, post mortem, as chorea*, it is exceptional to find the heart healthy ' Since these patients were studied before Aschoff had described the lesion considered pathognomonic of rheumatic fever and the techniques for microscopic study were not as advanced as they are today the percentage of cases showing evidence of rheumatic fever may have been even greater Although no series of fatal cases of chorea have been reported in recent years the scattered reports indicate that the great majority show evidence of rheumatic carditis or valvular disease Furthermore, the type of heart disease which the patient with so called pure" chorea develops, is indistinguishable clinically and pathologically from that resulting from rheumatic fever

Clinical studies made on large groups of rheumatic children show that a high per cent suffer from chorea at some time, and also that the majority of patients with chorea eventually show other manifestations of rheumatic fever Jones and Bland[18] in a study of 1,000 consecutive young rheumatic and chorea patients followed for an average of 8 years found that 518 (51 8 per cent) had only rheumatic fever 348 (34 8 per cent) had rheumatic fever and chorea and 134 (13.4 per cent) had chorea alone or so called pure chorea Of 316 patients who exhibited only chorea at the onset of their disease, 134 (42 per cent) failed

to show any other evidence of rheumatic fever while the remaining 184 (58 per cent) subsequently developed other rheumatic manifestations. In another 164 patients chorea occurred subsequent to the onset of their rheumatic fever. In other words of 48[illegible] patients who suffered chorea 134 ([illegible]8 per cent) exhibited no other evidence of rheumatic fever, whereas the remaining 348 (72 per cent) had other rheumatic manifestations either before or following the chorea attack. These figures are not out of line with those reported by other workers. Wilson Lingg and Croxford[1] found that 4[illegible] per cent of their rheumatic children had chorea. Coombs[34] reported that on careful analysis of [illegible]7 cases of chorea 76 per cent had other manifestations of rheumatic fever. Of 416 young rheumatic subjects studied by Ash[39] 34.4 per cent developed chorea and of 138 chorea patients 7[illegible] per cent at some time showed other evidence of rheumatic fever.

It is well known that an appreciable number of all attacks of chorea (15 to [illegible]0 per cent) either precede or follow immediately a bout of rheumatic fever the manifestations of one condition gradually subsiding while those of the other make their appearance. In such cases it is more common for the chorea to follow on the heels of the rheumatic episode. It is not unusual however to find evidence of active rheumatic fever during the attack of chorea. In about [illegible]0 to 30 per cent of cases no other manifestations of rheumatic fever appear in the remaining 50 to 6[illegible] per cent the rheumatic fever either precedes or follows the chorea by a number of months or years.

The incidence of heart disease in chorea and rheumatic fever as reported by various workers is shown in Table I. It is clear from this Table that about 45 per cent of all cases of chorea develop heart disease which is indistinguishable clinically and pathologically from that found in rheumatic fever. It is also apparent that the incidence of heart disease in cases of so called pure chorea is appreciably less than in those who also had other manifestations of rheumatic fever the incidence of heart disease in the latter group approximating that for cases of rheumatic fever alone. These data indicate that the patient with pure chorea has a good chance of escaping valvular heart disease while the appearance of other manifestations of rheumatic fever very definitely increases the risk of permanent valve damage to the heart.

From the preceding discussion it is apparent that chorea and rheumatic fever are very closely associated. It is still not possible to say with finality that all chorea is a rheumatic manifestation. However it is impossible at present to differentiate the non rheumatic chorea from the

rather dull intellectually Others do not agree with this concept and hold that the dull may be affected as frequently as the more sensitive and intelligent child

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rheumatic chorea clinically if such a separation exists Most workers who have followed patients with chorea for long periods of time know that it is not unusual to see a child who has had one or more attacks of "pure" chorea develop other manifestations of rheumatic fever and eventually die of that disease or of its sequelae In the present author's opinion until more definite evidence can be presented to the contrary all Sydenham's chorea should be considered as a mild manifestation of rheumatic fever The etiology of rheumatic fever has been considered in a separate chapter of Oxford Medicine (Chapt II Vol V) and will *not be discussed here*

Pathology

The pathology of Sydenham's chorea is poorly understood A review of the literature reveals a diversity of findings at post mortem as well as many different opinions attempting to explain the signs and symptoms on the basis of the pathological changes described There is no pathognomonic brain lesion and the lesions found in fatal cases may appear remarkably insignificant

Frequently there is hyperemia of the brain to a varying degree and occasionally this may be the only abnormality At times small cell infiltration throughout the brain as well as perivascular infiltration with lymphocytes and other mononuclear cells may be seen In some cases intimal proliferation of the medium sized arteries and capillaries of the brain with or without thromboses occurs These vascular changes are similar to those described by Von Glahn and Pappenheimer[46] in rheumatic fever Degeneration of nerve calls of varying degrees also may be found These abnormalities are usually most marked in the cerebral cortex and the basal *ganglia especially the neostriatum* but may also occur in the cerebellum When present the changes are not typical and similar changes may be demonstrated in patients dying as the result of other types of infections The mildness of the lesions frequently found probably explains the reversibility of the process without sequelae Also functional changes may well occur which cannot be demonstrated by present day histological techniques

Although the anatomical findings may be diffuse it seems probable that the motor cortex is the area directly responsible for the production of the spontaneous movements It appears likely that the changes found elsewhere in the brain *render the cortex more excitable than normal*

TABLE I

THE INCIDENCE OF HEART DISEASE IN CHOREA AND RHEUMATIC FEVER AS REPORTED BY VARIOUS AUTHORS IN THE LITERATURE

Authors	*Pure Chorea*				*Chorea and Rheumatic Fever*				*All Chorea*				*Rheumatic Fever Without Chorea*			
	No Ht Dis	*per cent*	*Ht Dis†*	*per cent*	*No Ht Dis*	*per cent*	*Ht Dis*	*per cent*	*No Ht Dis*	*per cent*	*Ht Dis*	*per cent*	*No Ht Dis*	*per cent*	*Ht Dis*	*per cent*
Ma ke e S R po t C llecti e I tigat C nm tt Br t M d As c 1887					57	49 1	59	50)	/8	(6 3	141	13 7				
O l W 1894									68	48 6	7	51 4				
Th er W S 1906	513	93 0	105	1 0	112	65 5	59	34 5	498	[illegible]	191	7 7				
Alt I A and I n A 1916									153	67 7	73	1 3				
K lk H 1919									87	7 3	23	7 7				
Str g C F 19 3									55	55 0	45	45 0	119	6 0	7	39 0
C C F 19 4									56	56 0	44	44 0	25	5 0	5	5 0
P t n I J 19 5									95	43 6	[illegible]	5[illegible]				
M kie T T 19 6									3	48 5	34	51 5	116	31 7	250	68 3
M r lall R 19 8									27	40 3	40	59 7				
W l o M C Lingg C nd Cr f d C 19 8	5	0 0	20	80 0												
Wall ce H I 1933									127	59 5	90	41 5				
S h a H and L der S D 1935	17	7	8	77 3												
Jo s T D a l Bl t F F 1935	130	97 0	4	3 0	93	7 0	55	71 0	2 3	46 0	59	54 0	71	14 0	447	86 0
A h R 1936	39	86 7	6	13 3	31	28 7	77	71 3	70	45 8	83	54	8	9 5	196	70 5
Pa h P L T ran L M and St rr S 1937	37	47 4	41	5 6	8	1 5	6	76 5	45	40	67	59 9				
S tt n L P and Dodg K G 1938	74	81 3	17	18 7	159	4 3	17	57 7	33	49 9	234	50 1	164	9 0	4 1	80 0
U h S J 1938	41	73	15	6 8	17	34 7	32	65 3	58	55	47	44 8				
H fley O F 1940									389	57 9	99	4 1	496	36 7	838	63 3
W l m A C and W el m B C 1944									161	7 9	(0	7 1				
Jac b n F 1946									9	[illegible]0	71	71 0				
TOTALS	856	76 3	66	23 7	477	39 7	7 5	60 3	684	55 0	194	45 0	106	31 6	99	68 4

I e t a d e t p t ts wlo l l Syl nh m s cl a w th t ny ther n fe t t s f rl nate f y
All ch a l t p t nts who h d Syl h m ch a l f t e of oth she m t c m n f tat s

† nl c t a n l t d

†† nl t h t d

constantly flung about In severe cases the movements may toss the patient about the bed leading to severe bruises and injury unless he is cared for properly Attacks may be of all grades of severity some being so mild as to be barely detectable and often missed by those unfamiliar with the disorder

When the condition affects one side of the body only it is commonly referred to as hemichorea The muscles of the face are involved often giving rise to facial grimacing and making it appear as if the patient were making faces On occasions facial expression may change suddenly from one of solemnity to laughter or frowning In severe cases the muscles of the pharynx and larynx may be affected causing difficulty in swallowing and speaking Occasionally the sensitive child conscious of his inability to speak clearly may refuse to talk and thus is believed to be aphasic The protruded tongue usually is jerked into the mouth when the command is given In very severe cases even the muscles of respiration may be involved giving rise to a jerky type of respiration

By willed efforts the spontaneous movements of one part may be controlled to a degree but when such attempts are made the movements of another part usually become more marked During sleep the spontaneous movements generally cease however in severe cases it may be difficult to get the patient to sleep because of the violent jerks Chorea rarely if ever causes loss of sphincter control nor does it affect the extra ocular muscles The sensibility of the patient is not disturbed nor are the special senses involved

The incoordination in chorea is due in large part to the voluntary movements being interrupted by the unwilled spontaneous movements In carrying out acts such as reaching for a glass of water the arm and hand may be repeatedly jerked out of its course so that the patient misses the object or knocks it over Coordinated and fine movements such as are necessary for sewing and writing are impaired also and one may obtain a written record of the course of the disorder by having the patient write his name at intervals In addition to this there also appears to be a lack of smoothness in the voluntary movements and there is a tendency for the patient to overreact with apparent clumsiness when requested to perform a simple act such as getting into bed

Some muscular weakness of the involved parts frequently is demonstrable Contractile power often is weakened and poorly sustained The poorly sustained grip one of the most characteristic signs of mild chorea probably is due in large part to the spontaneous movements which cause the patient to relax his grip momentarily This is commonly manifest

and that the slightly altered cortical cells may discharge spontaneously giving rise to the choreiform movements The electroencephalographic findings would tend to support such a view[47 48]

As previously stated the great majority of patients dying with chorea show definite evidence at autopsy of rheumatic fever or rheumatic heart disease The pathology of this disease is adequately described in Chapt II of Vol V

Symptomatology

The patient usually a child between the age of 5 and 16 years, is brought to the doctor because of increasing nervousness fidgetiness and irritability The onset usually is insidious, and the condition very gradually increases in severity over a period of days or weeks, in a small number of patients, however, the onset may be abrupt with rapid progression Prodromata such as inattentiveness, irritability, sulkiness, easy fatiguability, anorexia and loss of weight may be noted Frequently there is a past or family history of rheumatic fever or chorea On close questioning it may be brought out that the onset of the attack was preceded 1 to 3 weeks by an upper respiratory tract infection, sore throat, scarlet fever or the patient may be convalescing from an attack of rheumatic fever In about one quarter of the cases other manifestations of active rheumatic fever such as mild joint pains, epistaxis low grade fever, erythema marginatum (annulare) or subcutaneous nodules will be associated with the chorea Whether the attack is one of so called "pure chorea or was preceded or is accompanied by other manifestations of rheumatic fever the choreic signs and symptoms are the same

Chorea is essentially a disorder of the motor system with associated emotional instability The three cardinal affections of the motor system are (1) spontaneous movements (2) incoordination of voluntary movements and (3) muscular weakness The spontaneous movements are the most conspicuous feature They are characteristically quick, brief jerky, irregular, purposeless movements, usually very mild at the onset amounting to nothing more than an occasional twitch of the affected part Early they are confined usually to one extremity, one arm and leg or the face but may involve all parts of the body As the condition progresses the movements involve other parts become larger and more frequent so that at the height of the attack the arms and legs may be

constantly flung about In severe cases the movements may toss the patient about the bed leading to severe bruises and injury unless he is cared for properly Attacks may be of all grades of severity some being so mild as to be barely detectable and often missed by those unfamiliar with the disorder

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on the part of the patient by his tendency to drop objects In cases of hemichorea weakness of the affected side usually can be clearly demon strated Infrequently weakness may be the most pronounced symptom so the patient complains of inability to use one arm or leg The weak extremity will hang at the side or be dragged along on walking Very rarely weakness will be so marked that the patient will lie entirely motionless *paralytic chorea* or *chorea mollis* Spontaneous movements will be correspondingly decreased in those parts showing the most marked weakness

Emotional instability commonly is present The patients are frequently irritable inattentive or sulky and crying or laughter may occur with inadequate reasons In very severe cases delirium and excitement amounting to mania may be seen, *chorea insaniens* It is also notable that when patients with chorea are subjected to mild stress of any type, the manifestations usually become more prominent

On examination the deep tendon reflexes may be variably altered and also may vary from time to time They may be normal exaggerated, diminished or rarely absent Frequently one may find a sustained type of knee jerk or obtain a pendulum effect The pendular type of knee jerk and diminished reflexes usually are associated with hypotonia which is present so frequently in chorea The hypotonia also can be demon strated by the increased range of the joints on passive motion The superficial cutaneous reflexes are intact Very rarely plantar stimulation may elicit an extensor response Rapid rhythmic alternating movements are poorly performed When the hands are held outstretched or extended above the head the palms commonly turn outward the *pronator sign*, or the hands may assume the position of flexion at the wrists, hyperextension at the metacarpophalangeal joints with extension of the fingers abduction and dipping of the thumbs

The course of chorea usually is afebrile except in severe cases or when there are other manifestations of active rheumatic fever A rapid heart rate is often indicative of an accompanying carditis The total leucocytes and differential counts usually are normal in the uncompli cated cases Very mild grades of normochromic or hypochromic anemia may be found but more severe grades of anemia generally indicate rheumatic activity as does an elevated erythrocyte sedimentation rate or electrocardiographic abnormalities On lumbar tap the pressure and manometrics are normal with an entirely normal spinal fluid or at most a very slight increase in mononuclear cells.

Most cases of severe chorea show electroencephalographic abnormalities while mild cases may show little or no change The abnormalities are not specific and consist essentially of a decrease or absence of normal alpha rhythms with the presence of runs of continuous delta or slow wave activity of increased amplitude[17, 18] In patients with hemichorea there is usually greater abnormal activity from the contralateral hemisphere Usher and Jasper were unable to differentiate the pure choreas from those associated with rheumatic fever on the basis of the electroencephalographic findings and believe the abnormal electroencephalogram argues against the importance of psychogenic factors in chorea They also found that clinical improvement was definitely correlated with decreased abnormality in the electroencephalogram

Diagnosis

The usual case of Sydenham s chorea generally offers little difficulty in diagnosis The history together with the characteristic signs and symptoms occurring in a rather limited age group and its close association with other manifestations of rheumatic fever help make the diagnosis relatively easy There are certain conditions however which may simulate chorea and from which it should be differentiated

Tic or *habit spasm* is characterized by persistently repeated clonic motions which are well localized and repetitive in detail in contrast to the purposeless irregular non repetitive and non localized movements of chorea *Acute encephalitis* may at times give rise to choreiform movements however the history of onset together with the presence of pupillary changes, cranial nerve abnormalities meningeal signs and its course generally serve to distinguish it from chorea

Cerebral palsy patients occasionally may exhibit spontaneous involuntary movements resembling those of chorea These movements usually are more athetoid than choreiform in character Also the history dating from infancy together with the findings of pyramidal tract disease makes the differential diagnosis *Hysteria*, because of the exhibition at times of spontaneous movements may be mistaken for chorea Here the movements are usually more 'purposive' and patterned than in chorea also the history with the marked emotional background the presence of anesthesia and other hysterical manifestations differentiates it from chorea

Dystonia musculorum, a rare chronic disorder, is characterized by irregular involuntary, clonic contortions of the trunk and proximal muscles. Although the disease frequently begins at about the same age as chorea the symptoms usually are not manifest while the patient is at rest but are initiated by voluntary movement. On walking the patient's body usually is twisted backward and forward in a rather bizarre manner.

Huntington's chorea is a rare familial disease which rarely becomes manifest before the age of 30 years, an age at which chorea is unusual. The history, together with the signs of mental deterioration, readily distinguish it from Sydenham's chorea. *Congenital chorea* is present in early infancy and varies little with maturity. The movements are essentially the same as seen in Sydenham's chorea and are present both during rest and voluntary activity. In its pure form there is no spasticity. The child with congenital chorea usually can perform certain complicated acts such as writing his name, which is difficult for the child with Sydenham's chorea.

Progressive hepatolenticular degeneration (Wilson's disease) is a rare familial disease characterized by lenticular degeneration and cirrhosis of the liver. The spontaneous movements in this condition usually begin as tremors exaggerated by voluntary motion, but the patient may exhibit athetoid and spasmotic movements. The presence of hypertonia, liver disease and the Kayser-Fleischer corneal ring serve to differentiate it from chorea.

A more difficult problem than that of distinguishing chorea from other maladies which may exhibit similar spontaneous movements is that of deciding definitely whether a known rheumatic child has very mild chorea or is merely hyperactive. At times only by repeated observations can the diagnosis be established in such cases. Undoubtedly many cases of very mild chorea are missed by inexperienced observers and those not alert to the possibility. It also may be equally difficult to be certain when an attack of chorea has completely subsided.

Prognosis

Chorea per se is rarely fatal. In the very violent cases however death may result from exhaustion alone. Usually death in the choreic patient results from associated rheumatic fever and is largely dependent upon the degree of cardiac involvement. In the past other complicating

infections such as pneumonia septicemia etc were responsible for death in a certain number of patients with chorea but now these infections generally can be controlled by the proper antimicrobial therapy

The average attack of chorea usually runs a course of 6 to 12 weeks with variations from a few weeks to many months or even a year or more The length of the attack cannot always be correlated with the severity for the mild cases may persist for months while the severe attack may subside completely within a few weeks

Cardiac damage in the form of rheumatic heart disease is the only permanent sequela of Sydenham s chorea The mitral valves are most often affected and in the present author s opinion the clinical evidence of valve damage following chorea is frequently very insiduous and may not be evident for several years The risk of permanent cardiac injury following an attack of chorea is increased by the occurrence of other evidence of rheumatic infection The patient who has chorea alone without other manifestations of rheumatic fever stands a good chance of escaping cardiac damage On the other hand when other evidence of active rheumatic infection is present the incidence of cardiac sequelae approaches that for patients with rheumatic fever alone

Chorea tends to recur frequently in childhood, after puberty recurrences are much less frequent From a total of 2 395 cases collected by the present author from the literature it was found that 63 per cent suffered one attack 2 per cent two attacks and 15 per cent had three or more attacks It is not unusual to see patients who have had six or seven attacks of chorea Some workers believe that repeated bouts of chorea even in the absence of other rheumatic manifestations lead to an increased incidence of heart disease Until more patients have been carefully followed through repeated attacks of pure chorea this statement cannot be verified

TREATMENT

In the treatment of Sydenham s chorea there are three important facts which should be kept in mind (1) that chorea is not a disease entity but a symptom complex which at present should be considered a mild manifestation of rheumatic fever (2)that it is rarely fatal per se and its course is essentially self limited and (3) that there is no known specific treatment

Every patient should be studied carefully for other evidence of active rheumatic fever particularly carditis and if present proper therapy

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tions such as measles are often beneficial in relieving the manifestations of chorea Von Kern[17] in 19 3 reported some success in the treatment of three cases of chorea following the injection of sterile milk but failed to attribute the improvement to fever In 1930 Mas de Ayala[28] inoculated a patient suffering from chorea with *Treponema hispanicum* to produce fever Sutton[1] in 1931 first employed typhoid paratyphoid vaccine intravenously to produce febrile reactions in chorea patients Since this time other methods of inducing artificial fever by electrical *means such as the Kettering hypertherm have been introduced* and used in the treatment of chorea with success One of these methods is preferable to the use of triple typhoid vaccine since the temperature can be more easily controlled and the patient made more comfortable during the induction and course of the fever On the other hand one needs special apparatus and a trained operator for this type of treatment In either case fever therapy should be given only under the supervision of an experienced person It should be remembered also that fever therapy is a vigorous form of treatment and cannot be considered entirely free of danger Patients with badly damaged hearts and those with severe carditis should not be subjected to fever therapy Mild carditis however cannot be considered a contraindication to its use Patients receiving fever therapy should be carefully checked before each treatment and the schedule promptly interrupted if necessary

If triple typhoid vaccine is employed the initial dose should be 0 05 to 0 1 ml of a typhoid paratyphoid vaccine containing 1 000 million typhoid bacilli and 750 million each of paratyphoid A and paratyphoid B bacilli per ml The injection is given intravenously in the morning after a light breakfast and the patient allowed only warm tea or sweetened fruit juice during the reaction To be effective temperature rises of 104° to 106°F per rectum must be secured If the temperature exceeds 106 F per rectum 0 6 gm of aspirin should be administered and an ice cap applied to the head if this is not effective in lowering the temperature a tepid sponge should be given With each succeeding treatment it is usually necessary to approximately double the preceding dose in order to secure an adequate febrile reaction Treatments are given daily or every other day according to the condition of the patient and should be continued if possible until all signs of chorea have subsided According to Sutton and Dodge[52] approximately 5 to 6 treatments are required for the usual mild cases 7 to 8 for moderately severe and 8 to 10 for severe cases

should be instituted in addition to any special treatment the choreic symptoms demand Whether or not the patient exhibits other signs or symptoms of active or inactive rheumatic fever his long term care should be the same as that for any other known susceptible rheumatic subject The treatment of rheumatic fever has been adequately described in Chapt II of Vol V and only those special therapeutic measures of value in the treatment of the choreic symptoms will be discussed here

Since chorea is rarely fatal and is essentially self limited vigorous forms of therapy and types of treatment which are potentially dangerous usually are unjustified

Bed rest in a quiet room with properly trained nursing care is most important in the treatment of the acute attack Patients cared for on the open ward or at home in the presence of other children and frequent visitors generally do not respond as well as those nursed in a quiet room The nurse or person responsible for the care of the patient should be adequately informed regarding the nature of the disorder, especially in regard to the emotional aspects The diet should be nourishing with added vitamin B complex particularly in the case of those patients who are undernourished Patients who have difficulty in feeding themselves should be fed Occasionally patients with very violent attacks and those with difficulty in swallowing may have to be fed through a nasal tube In severe cases it is also necessary to pad the sides of the bed to prevent the patient from injuring himself and to take the proper precautions to keep the patient from falling out of bed

Sedatives usually are helpful in controlling the movements and giving the patient rest mentally as well as physically Phenobarbital in doses of 0 015 gm to 0 10 gm or chloral hydrate, 0 5 gm to 1 0 gm may be given three or four times daily Sodium bromide in equal dosage may be added to the chloral hydrate if desired In more severe cases hyoscine hydrobromide 0 4 mgm to 0 6 mgm may be used In the very severe cases in which incessant movements prevent rest intravenous amytal or paraldehyde or ether in oil by rectum may be employed In these violent cases it is necessary that the patient be given adequate rest

For the mild and often for the moderately severe chorea patient rest in a quiet room with mild sedation good nursing care and a well rounded nutritious diet is frequently all that is necessary In the more severe cases or in those cases which do not respond to the above regime alone, fever therapy may be used

Fever therapy is often very effective in arresting the choreic symptoms It has been known for many years that intercurrent febrile infec

tions such as measles are often beneficial in relieving the manifestations of chorea. Von Kern[49] in 19 3 reported some success in the treatment of three cases of chorea following the injection of sterile milk but failed to attribute the improvement to fever. In 1930 Mas de Ayala[50] inoculated a patient suffering from chorea with *Treponema hispanicum* to produce fever. Sutton[1] in 1931 first employed typhoid paratyphoid vaccine intravenously to produce febrile reactions in chorea patients. Since this time other methods of inducing artificial fever by electrical means such as the Kettering hypertherm have been introduced and used in the treatment of chorea with success. One of these methods is preferable to the use of triple typhoid vaccine since the temperature can be more easily controlled and the patient made more comfortable during the induction and course of the fever. On the other hand one needs special apparatus and a trained operator for this type of treatment. In either case fever therapy should be given only under the supervision of an experienced person. It should be remembered also that fever therapy is a vigorous form of treatment and cannot be considered entirely free of danger. Patients with badly damaged hearts and those with severe carditis should not be subjected to fever therapy. Mild carditis, however, cannot be considered a contraindication to its use. Patients receiving fever therapy should be carefully checked before each treatment and the schedule promptly interrupted if necessary.

If triple typhoid vaccine is employed the initial dose should be 0.05 to 0.1 ml. of a typhoid paratyphoid vaccine containing 1,000 million typhoid bacilli and 750 million each of paratyphoid A and paratyphoid B bacilli per ml. The injection is given intravenously in the morning after a light breakfast and the patient allowed only warm tea or sweetened fruit juice during the reaction. To be effective temperature rises of 104° to 106°F. per rectum must be secured. If the temperature exceeds 106 F. per rectum 0.6 gm. of aspirin should be administered and an ice cap applied to the head; if this is not effective in lowering the temperature a tepid sponge should be given. With each succeeding treatment it is usually necessary to approximately double the preceding dose in order to secure an adequate febrile reaction. Treatments are given daily or every other day according to the condition of the patient and should be continued, if possible, until all signs of chorea have subsided. According to Sutton and Dodge[51] approximately 5 to 6 treatments are required for the usual mild cases, 7 to 8 for moderately severe and 8 to 10 for severe cases.

If one of the electrical methods for inducing artificial fever is to be used, then the patient may be given short courses of fever of 2 to 3 hours duration daily or every other day, or longer courses of fever of 6 to 8 hours may be given biweekly. In either case the temperature should be maintained between 104° and 105 F per rectum for the period chosen. Provided the patient's condition permits, the treatments should be continued until the chorea has completely subsided or until at least 50 hours of therapy have been given. Often marked improvement in the choreiform movements is observed after the first or second treatment following either form of fever therapy. Recurrences of the chorea, however, are not uncommon.

Taussig[51] has used starvation therapy and a ketogenic diet for the treatment of chorea. She believes the four day starvation period is quite important, indeed more important than is the ketogenic diet. It is her strong impression that chorea responds to it quite as well as to typhoid vaccine therapy and it is both simpler and safer.

Arsenic in the form of Fowler's solution (solution of potassium arsenite) first recommended for the treatment of chorea minor by Thomas Martin in 1879[5], is no longer advised. There is no evidence that it is effective in relieving the choreic symptoms, and it is a potentially dangerous drug. Nirvanol (phenyethyl hydantoin) introduced by Roeder in 1919[56] for the treatment of chorea likewise is not advised. The beneficial effects of this drug on chorea are probably due largely to the febrile reaction it produces, nirvanol sickness. Nirvanol is dangerous in that it may cause exfoliative dermatitis, agranulocytosis and other undesirable toxic effects. Some deaths have been reported following the use of nirvanol. Streptococcal vaccines and antisera have no specific effect on chorea and what benefit they may produce is probably the result of non specific protein reactions with fever. Repeated lumbar punctures with drainage are traumatic and unjustified, until more evidence is presented that they are beneficial.

Salicylates and aminopyrine appear to have no effect on the course of chorea, however these drugs may be employed to control other rheumatic manifestations appearing during the attack of chorea.

Chorea Associated with Pregnancy (Chorea Gravidarum)

Chorea associated with pregnancy is a rare condition and in the past

was considered to be a serious complication carrying with it a high mortality Willson and Preece in their very able review of the subject found in a survey of a number of hospitals in this country that the number of cases of chorea gravidarum varied between 1 in 846 pregnancies to 0 in 10 000 More recently Hamilton and Thomson[x] reported that Irving found only 4 cases in 39 000 pregnancies at the Lying in Hospital in Boston and Stander[59] reported 12 cases in 34 569 pregnancies at the New York Hospital

The *relationship of chorea gravidarum to Sydenham's chorea* has been the subject of much controversy Willson and Preece's study led them to conclude that the chorea occurring during pregnancy is identically the same as Sydenham's chorea modified slightly in certain respects by its association with pregnancy With this conclusion most workers today are in agreement However a few believe it to be an entirely different entity dependent directly on pregnancy for its causation Willson and Preece's conclusion is based on clinical and pathological data obtained from an analysis of 951 cases of chorea gravidarum It is of some interest that about one third of these cases showed evidence of cardiac disease and 87 per cent of those coming to autopsy had rheumatic heart disease These figures are in good agreement with those reported for Sydenham's chorea

The possible importance etiologically of emotional factors has been considered in chorea gravidarum as it has in Sydenham's chorea Weigner[60] analyzed approximately 950 reported cases of chorea occurring during pregnancy in addition to reporting one case of his own He found that 137 of these cases had significant precipitating emotional factors and that the incidence of previous chorea and heart disease was significantly less in these cases than in those in which precipitating emotional factors were not present From this he suggests that chorea gravidarum should not be considered a clinical entity but that it may be precipitated by various factors

Chorea gravidarum occurs predominantly in young women the average age in the cases analyzed by Willson and Preece being 24 years It is likewise much commoner in primiparas the complication very rarely occurs in later pregnancies unless the patient experienced it with her first pregnancy The tendency to recurrence in more than one pregnancy however is common

A previous history of chorea or rheumatic fever or both is common in patients with chorea gravidarum Willson and Preece found that more than one half of the cases analyzed by them gave a history of a previous

attack of chorea more than one-third a previous attack of rheumatic fever more than one-fourth had had both diseases previously, and in about 1 case in 10 there was both rheumatic fever and chorea in the same pregnancy. Like Sydenham's chorea chorea gravidarum appears to be much less common in the negro.

The *clinical signs and symptoms* of the chorea associated with pregnancy are identical with those of Sydenham's chorea. In the great majority of cases the chorea begins during the first trimester but may begin at any time during the pregnancy and rarely is present before conception occurs. In many instances the chorea subsides before delivery but if not it often does very soon after delivery; however, occasionally it may persist for months afterwards.

The *prognosis* for patients with chorea gravidarum is now good, the high mortality rates noted in the older literature probably were largely due to attempts to interrupt the pregnancy with the lack of present day asepsis. It is also probable that the chorea associated with pregnancy like uncomplicated Sydenham's chorea is less severe today than it was fifty years ago. The presence of other manifestations of rheumatic fever particularly carditis and evidence of marked cardiac damage, makes the prognosis worse.

The *treatment* of chorea gravidarum should be marked by conservatism. The choreic symptoms should be treated in the same manner as indicated for Sydenham's chorea except that fever therapy is contraindicated. Those patients with severely damaged hearts and chorea should be interrupted early in pregnancy or later handled in the manner indicated for patients with rheumatic heart disease and pregnancy together with any special treatment required for the chorea. In general the patients should be handled jointly by the internist and obstetrician and the course of therapy to be followed determined on the merits of the individual case. The question of future pregnancies should be decided largely on the basis of the degree of permanent cardiac damage.

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CHAPTER XXXIII

THE DYSTROPHIES AND ALLIED DISORDERS OF MUSCLES

BY REDVERS IRONSIDE

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Introduction

The term *muscular dystrophy* is widely used to refer to certain markedly hereditary or familial diseases of obscure etiology. Clinically there are no clear lines of demarcation between different types of dystrophy but certain combinations of symptoms recur in which the muscular affection is specially localised and stereotyped in its manifestations. These syndromes occur regularly enough to be called separate diseases.

At this stage when our knowledge of the pathology is so meagre no satisfactory attempt to classify these diseases is possible. There are broadly two groups.

I *Myopathic Dystrophy* — The essential pathology is a primary degeneration of the contractile elements of the muscle fibrils themselves. Lesions in the nervous system are absent. Such myopathic dystrophies often are inherited or familial but do not show themselves until childhood or early adult life. Occasionally they may appear in late adult life. Anatomically the diseased muscle fibrils may present many variations in size, shape and structure. Atrophy and hypertrophy of the muscle fibrils occur. When the atrophied muscle fibrils are replaced by connective tissue and excessive deposit of fat the condition is known as pseudo hypertrophy. Certain symmetrical groups of muscles tend to be affected regularly. There is always an associated disturbance of muscular function in most cases simple weakness of contraction; muscles showing no alteration in their total mass may exhibit considerable impairment of function. Alterations in the excretion of creatin and creatinin occur but these simply are secondary to the degeneration of the sarcoplasm and do not indicate any primary disorder of metabolism.

An example of myopathic dystrophy is the progressive muscular

the work of Stanley Barnes on a myopathic family (see dystrophy of Barnes) and the studies of K. Nissen on myotonia congenita

Julia Bell and Macklin have published excellent accounts of the inheritance of the myelopathic peroneal muscular atrophy. These writers working with scattered families many of whose antecedents are deceased have produced most carefully worked out pedigrees. But one is immediately impressed with the difficulty of fitting the type of inheritance into any complete genetic scheme. The inheritance of most of the dystrophies is extremely complex; the Mendelian ratios in the human are never exact, only approximate, and variability in the mode of inheritance even in the disease itself may be observed in the same stock.

Mendel showed that unit characteristics are transmitted in simple mathematical ratios. As the result of cytological and genetic studies it is believed that inherited characteristics are conveyed by the genes residing in the chromosomes of the germ cells. Subjects receiving identical genes from each parent are termed homozygous and those who have unlike genes are heterozygous. Similar genes are termed autosomal genes. Alternative genes are known as allelomorphs.

Some genes always give rise to the characteristic which they carry and are called dominant. Others are latent unless they are paired with identical genes and hence are called recessive. Some genes are contained within the same chromosomes which determine sex, and the characteristic which they convey therefore will be sex linked or limited.

Where the characteristic giving the disease is dominant the disease can be transmitted by one parent alone. Recessive inheritance may be suspected when the dystrophy appears in a child or children whose parents both seem normal. The disease only appears when the child inherits an abnormal gene from each parent, both of whom are to all appearances normal. Both parents are heterozygous for the defect, but the corresponding gene for normality renders that for the defect latent. Where the inheritance is sex linked as in the pseudo hypertrophic muscular dystrophy, the disease commonly is transmitted by the unaffected females. A typical orderly pedigree of this nature will show affected males and no affected females.

In human inheritance a complicating factor is that the same disease may be transmitted as a dominant in one family and in another family as recessive, and in the same family the characteristic manifestation of the family disease may differ in different generations (see dystrophy of Barnes).

Polymorphism.—The disease in a dystrophic pedigree tends to reproduce itself in succeeding generation in very similar form. Not only the age of onset and the distribution but also the order of progress of

dystrophy where the degeneration is an actual alteration in the sarco plasm of the muscle fibrils In some cases this primary degeneration of the sarcoplasm is accompanied by an added abnormality at the myoneural junction Clinically this gives rise to a curious increased muscular tonicity with difficulty in initiating contraction and slowness in relaxing known as myotonia Examples of diseases in this group are *dystrophia myotonica* and *myotonia congenita*

Outside of the muscular system dystrophic symptoms may be present elsewhere e g adiposity general wasting baldness cataract and mild occlusion of the teeth It is clear that many of these latter symptoms are referable to endocrine disturbance We do not at present under stand the relationship of the ductless glands to muscular dystrophies

II *Myelopathic Dystrophy* — In this group of hereditary and familial diseases the muscular affection is accompanied by gross histological changes in the ventral horn cells of the spinal cord or in the peripheral nerves Peroneal muscular atrophy progressive hypertrophic polyneuritis and the infantile forms of spinal muscular atrophy are examples of myelopathies

In reality there is no sharp division between myopathic and myelopathic groups for both types of disease may appear in members of the same family Moreover the myelopathic disease may be associated in certain families with one of the heredo familial system diseases of the neuraxis e g hereditary ataxia or hereditary spastic paraplegia Beimond has published cases from a stock affected by peroneal muscular atrophy where the exact disease was replaced in some members by an essential spinal cord disease resembling hereditary ataxia Other instances are recorded where cases of peroneal atrophy or progressive hypertrophic polyneuritis have been associated with congenital optic atrophy or with hereditary spastic paraplegia Thus all the heredo familial diseases of muscle and neuraxis seem to have biological relationships one with the other They all exhibit a premature dissolution of tissue with accompanying functional loss after a varying period of normal function this Gowers termed abiotrophy

THE INHERITANCE OF DYSTROPHIES

The dystrophies are markedly familial and hereditary but the study on the pedigrees of affected families presents great difficulties Many excellent genetic studies have been published Notable among these is the work of Professor Karl Pearson on progressive muscular dystrophy

acromegaly dystrophia adiposo genitalis and other indications of endocrine disorder are met with occasionally in conjunction with myopathic wasting The inherited defect responsible for the paralysis may be the cause also of the endocrine disturbance as a secondary and less important defect Some members of an affected stock may show only the endocrine symptoms and no muscular abnormality A special search always should be made amongst ancestors and collaterals to bring to light forms of aberrant defect suggesting a family trait not frankly dystrophic Such traits are absence of the sternal portions of the pectoralis major muscles small sterno mastoids large calf muscles weakness of the orbicularis palpebrarum muscles or absence of tendon reflexes

I MYOPATHIC DYSTROPHIES

PROGRESSIVE MUSCULAR DYSTROPHY

Synonym — Myopathy

Definition — A disease of the muscles characterised by a primary degeneration of the muscle substance independent of disease in the nervous system Clinically the cases are characterised by atrophy hypertrophy and pseudo hypertrophy and weakness of the muscles of the shoulder and pelvic girdles and of the proximal muscles of the limbs

According to the type of muscle disorder the group of muscles first attacked and the age of onset a number of types or syndromes have been described For clinical purposes it is convenient to differentiate (a) the pseudo hypertrophic dystrophy (b) the simple atrophic dystrophies including the juvenile type of Erb and the facio scapulo humeral type of Landouzy and Dejerine (c) sporadic and late cases (d) dystrophia hypertrophica musculorum (Spiller) (e) the distal dystrophy and (f) the dystrophy of Barnes The first second and third of these syndromes are not uncommon in neurological practice All the clinical types merge into one another Thus cases of the simple atrophic dystrophy sometimes manifest pseudo hypertrophy and various members of an affected stock may exhibit differing types of the disease

History

The first cases described of the disease were of the pseudo hypertrophic form Meryon in 1852 in a paper entitled on granular and fatty degeneration of the voluntary muscles described four cases with one autopsy of progressing muscular atrophy in brothers the sons of an

symptoms tends to be constant in the same stock Defective nutrition intercurrent illness and trauma may modify the age of onset Cases differing from the expected type occasionally occur a phenomenon known as polymorphism If a sufficiently large number of cases of such an affected stock can be studied these transitional or abortive cases will be found to be phases in the course of the family illness

Anticipation — The phenomenon of earlier age incidence of the disease in succeeding filial generations is known as anticipation It should be remembered that increased watchfulness in the parent or doctor will lead to early detection of symptoms and consequent earlier diagnosis Intelligent parents in a stock known to be affected become quick to detect in their children the signs of the disease they have learned to expect and dread

In pseudo hypertrophic muscular dystrophy typically the males only are affected and the disease is transmitted through unaffected females But we know that female children may manifest the disease also and the condition may be passed through an unaffected male as well as through an unaffected female carrier Analogous variations occur in the other myopathic and myelopathic dystrophies

The dystrophies are productive of a great deal of personal misery and economic distress in affected families Early death before the age of reproduction and poverty may cause extinction of the stock Karl Pearson writes On broad lines what comes out of pedigree enquiries is the fact that we are dealing with a tainted stock We shall achieve little by trying to save individual members from privation in regard to their procreative instincts by any doctrine of genes In that writer s opinion it is clearly the duty of all members of tainted stock to refrain from propagation We must inform the members of dystrophic families (1) that a healthy individual male or female may carry the disease (2) that the onset of the disease may be postponed to far beyond the reproductive age even as late as sixty years (2) that freedom in early life provides no security against the transmission of the disease to off spring (4) that second or subsequent children may suffer as well as the first born

The question of marriage is quite separate from that of procreation With present day knowledge of contraception it is safely possible for those individuals to marry

Adiposity and Associated Symptoms

The association of myopathic dystrophies with adiposity and other endocrine disturbances is noteworthy Stunted growth gigantism

current increase of fibrous tissue and fat. The pseudo hypertrophic muscles are the bulky muscles, viz. gastrocnemius, supraspinati and infraspinati, in which there is relatively a large amount of fat. Such pseudo hypertrophic muscles are liable to subsequent atrophy. Those muscles in which fibrous changes occur become hard and diminish in size. In some muscles, such as the lower half of the pectoralis major and the latissimus dorsi, the muscles seem to waste and disappear without the formation of fat or fibrous tissue. In other cases true hypertrophy may



Fig. 1 (a) Cross section of normal muscle. (b) Cross section of pseudo hypertrophic muscle showing atrophy and variation in size of the muscle fibrils and concurrent increase in fibrous tissue

be found in healthy muscles, perhaps of a compensatory character, to compensate for some other muscle weakened by the disease.

The earliest change in pseudo hypertrophic cases appears to be a swelling of the muscle fibril, which may measure three to five times the normal diameter (50 micra). The striations are less marked and there is increase in the nuclei of the sarcolemma sheath. Later there is an increase of connective tissue in the septa between the muscle bundles and the deposition of fat there. The fibrils themselves become narrow and irregular in shape and diminish in number. Fatty degeneration of the muscle fibrils themselves is not common, the usual change being a

English peer He stated clearly that no evidence of disease was found in the ganglion cells of the spinal cord and ventral roots and he gave drawings of the muscles presenting the appearances referred to in the title of his article In 1866 he published the account of a second autopsy stated that he believed the malady was an idiopathic disease of the muscles and pointed out the hereditary nature of his cases Duchenne of Boulogne in 1861 had described a disease which he called 'paralysie hypertrophique congenitale but it was not until 1868 that he recognised that the malady was independent of affection of the central nervous system and gave it the name of paralysie musculaire pseudo hypertrophique Gowers monograph on pseudo hypertrophic paralysis which appeared in 1879 remains the best account of the disease in the English language and in it he recognized that hypertrophy and atrophy may exist in different proportions

Erb of Heidelberg in 1883 described his juvenile type and Landouzy and Dejerine in 1884 described a form which differed from the juvenile type of Erb in that the facial muscles were affected In their report of a case which came to post mortem they showed that the spinal cord and peripheral nerves were intact The hereditary ' femoral type" was described by Mœbius in 1879

A distal type of myopathy was described by Gowers in 1902 and by Spiller in 1907 Spiller in 1913 described the true hypertrophic type dystrophia hypertrophica musculorum and Barnes in 1932 published an investigation into a dystrophic stock in which pseudo hypertrophy hypertrophy atrophy and myotonia appeared as phases of the family form of disease

Pathology

The diseased muscles to the naked eye may appear paler than normal The enlarged muscles in late cases of the pseudo hypertrophic dystrophy present on section the appearance of a greasy yellow mass of fat in which traces of muscular redness varying in amount can be perceived

In long muscles a fibrous change may be seen at the extremities in the neighbourhood of the tendinous attachment Abnormalities in the form of muscles apparently congenital in origin e g supernumerary digitations have been recorded

The heart muscle does not escape in the dystrophies but shows changes similar to those in the skeletal muscles but milder in degree

The microscopic appearances are the same in all forms of the disease (Fig 1) There is a progressive atrophy of the muscle fibrils with a con

current increase of fibrous tissue and fat The pseudo hypertrophic muscles are the bulky muscles viz gastrocnemius supraspinati and infraspinati in which there is relatively a large amount of fat Such pseudo hypertrophic muscles are liable to subsequent atrophy Those muscles in which fibrous changes occur become hard and diminish in size In some muscles such as the lower half of the pectoralis major and the latissimus dorsi the muscles seem to waste and disappear without the formation of fat or fibrous tissue In other cases true hypertrophy may

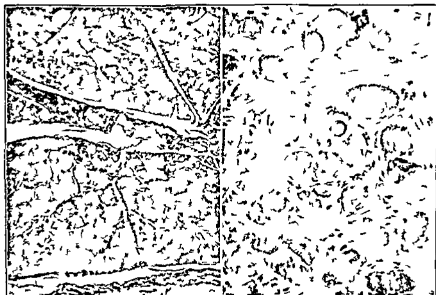


Fig 1 (a) Cross section of normal muscle (b) Cross section of pseudo hypertrophic muscle showing atrophy and variation in size of the muscle fibrils and concurrent increase in fibrous tissue

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granular degeneration hyaline change or vacuolation of the muscle fibre To account for the large number of small fibrils seen in later stages Marinesco suggests that the fibrils split longitudinally into smaller bundles of sarcostyles

Where there is true hypertrophy (dystrophia hypertrophica musculorum) there is actual increase in size of the muscle fibrils which may become three or four times the normal thickness

The muscle spindles and the myoneural junctions are intact even in advanced stages of the disease (Fig 1) Thickening of the wall and obliteration of the lumen of the small capillaries may occur and collections of small mononuclear cells may be seen in the adventitial lymph space The lumen of the capillary may be thrombosed

Gordon Holmes and others have described a definite diminution in number of the ventral horn cells There is a similar loss of fibres in the ventral roots and peripheral nerves Against the view that the cell changes are primary is the fact that the muscular changes are advanced and out of all proportion to those in the ventral horn cells It is probable that the cord changes are secondary to injury to the terminal branches of the axis cylinders which have been left exposed by the disappearance of their muscle fibre and are being surrounded in their place by fibrous connective tissue

There is no pathological evidence to support the hypothesis that disturbances in the autonomic system are responsible for muscular dystrophy

Chemical Changes in Myopathic Dystrophy

Normal muscle contains creatin phosphate phosphagen the breaking down of which apparently supplies the energy for muscular contraction As much as 98 per cent of the total creatin in the body is contained in the striated muscle During muscular contraction phosphagen is converted into creatin and phosphoric acid and these substances are excreted in the urine In the experimental animal when all the phosphagen is used up the muscle goes into rigor In normal muscle after contraction the creatin is almost immediately resynthesised The amount of creatin normally present in the whole blood is remarkably constant and varies from 4 to 5 mg per 100 c c most of this is in the blood cells but there is a little in the blood plasma

Creatin is present normally in the urine of children up to seven years of age 10 to 50 mgm per day and the amount excreted does not vary with the diet Various workers have demonstrated that creatinuria may

be present also when muscle is undergoing disintegration and it is found in women after pregnancy when the uterus is involuting

Normal male adults do not show creatinuria but the administration by mouth of the aminoacid glycin aminoacetic acid a precursor of creatin in the body may cause creatinuria Creatinuria in adults is observed also in wasting diseases e g progressive muscular atrophy diabetes ex ophthalmic goitre prolonged fevers and starvation

Of special interest is the fact that patients with muscular dystrophy show creatinuria If the patient is a child the creatinuria usually is in excess of the normal As a test of muscle function Milhorat and Wolff have devised the creatin tolerance test which in the writer s opinion is of doubtful clinical importance It tells little that cannot be revealed by a careful examination of the patient

Creatin Tolerance Test — If 1 32 gm creatin is given by mouth to healthy individuals on a diet free from creatin and creatinin and a constant water intake all or almost all of the test dose of creatin i retained in the body and none excreted in the urine Probably some is utilised immediately in the metabolism of phosphagen and the remainder is retained as such in the muscles Many patients with muscular dystrophy show impaired ability to retain the ingested dose of creatin The patient is given 1 32 gm of creatin by mouth and 24 hour specimens of urine diluted to the same volume each day are collected Creatin is estimated by the method of Benedict and expressed as a percentage of the amount administered The figure thus obtained is an expression of the ability to retain ingested creatin

As the muscle function fails so the creatin tolerance diminishes Milhorat and Wolff consider that the creatin tolerance is an index of the total mass of imperfectly functioning muscle rather than the amount of muscular atrophy They point out that patients with little or no visible atrophy may show evidence of generalised defect in muscle metabolism while cases with marked visible atrophy but with the bulk of the musculature functionally sound may show minimal evidence of disordered muscle metabolism In the advanced stages of muscular dystrophy all of the ingested dose of creatin is excreted in the urine

Similarly after ingestion of glycin aminoacetic acid say 10 gm twice daily by mouth for short periods such dystrophic patients show an increase up to 40 per cent in their constant creatinuria and a further decrease in creatin tolerance Thus in one case of dystrophy in a male child aged 10 years the urinary creatin after administration of 20 gm glycin daily rose from 226 to 850 mgm Glycin a precursor of creatin given by mouth thus leads to an increased formation of creatin in the

body which is excreted and not stored in diseased muscles This test is simply an indirect creatin tolerance test

Creatinin — The normal male adult excretes 23 mgm per kilogram of body weight of creatinin in the urine in 24 hours creatinin coefficient as the result of endogenous muscular metabolism There are considerable individual variations in the creatinin excreted in the urine but the amount eliminated by any one person is constant from day to day and independent of the total amount of nitrogen eliminated The readings are higher in those with well-developed muscles

In muscular dystrophy there is a progressive diminution in the elimination of creatinin compared with the average output for normal persons of the same age and sex

To summarise it may be said that in muscular dystrophy there is a progressive fall in the creatinin excretion and a slighter progressive rise in creatin excretion The decrease in one is not invariably followed by an increase in the other These changes are proportional to the amount of disturbance of muscle function that is present The creatin tolerance diminishes as the muscle function progressively fails Studies of the blood creatin in these conditions show no alteration from the normal This indicates that in muscular dystrophy there is a failure of storage in the damaged muscles

Normal muscle also contains glycogen which is converted into lactic acid after muscular contraction This lactic acid is neutralised by the alkaline muscle proteins and by alkaline salts after its formation Lundsgaard has shown that muscle poisoned with iodo acetic acid will contract anaerobically without the formation of lactic acid Lactic acid therefore does not seem to be essential for the contraction process

In muscular dystrophies disturbances of carbohydrate tolerance are met with not infrequently Hypoglycæmia and delayed utilisation of dextrose are reported most commonly but other anomalies of carbohydrate metabolism may be found There probably is defective glycogen storage in the damaged muscles Another possibility is that an associated endocrine abnormality may account for the alteration in oxygen tolerance

All these findings are clearly to be regarded as secondary to the muscular degeneration and in no way indicate a primary defect of metabolism Nevin has shewn that during contraction of dystrophic muscle creatin phosphoric acid breaks down and is reformed during rest to an extent only slightly less than normal Moreover he has found similar changes occurring in muscle undergoing atrophy secondary to nerve degeneration

Pseudo-Hypertrophic Dystrophy

Ætiology

Inheritance.—Sporadic cases occur occasionally. A family history of similarly affected brothers or sisters, however, is obtained usually. In an affected stock members of the same maternal sibship may have shown the malady in previous generations. As in hæmophilia and congenital night blindness, the disease is transmitted by the females only; the males who escape beget healthy children. The inheritance is indirect, recessive and sex-limited. As five-sixths of the cases of pseudo-hypertrophic dystrophy are dead before the age of 21 years, the stock tends to die out. Although blood grouping is not necessarily linked in inheritance with this dystrophy, there is a tendency for this to happen.

Sex.—Males and females are affected in the proportion of six males to one female. In girls the symptoms are said to be slighter and the course of the disease slower, while in boys the disease is severe and more rapidly fatal.

Age of Onset.—The age recorded when symptoms first became manifest will vary with the acuteness of observation of the parents or doctor. Symptoms usually show themselves before the age of six years. Occasionally symptoms are observed for the first time in middle life.

Symptoms

Weakness appears first in the pelvic girdle, later the shoulder girdle muscles are attacked. The first symptoms noticed by the parents are that the child is easily knocked over—"a puff of wind blows him down"—and that he has difficulty in rising from the ground. The child walks late, and it is noticed that his gait is peculiar. The patient stands with his shoulders and legs apart as if balancing himself. The backward carriage of the shoulders is associated with a remarkable lumbar lordosis which disappears when the patient sits or lies down. The balancing attitude when standing is accentuated when the patient walks. The feet are widely separated, and he walks with a rolling waddle, so-called "alderman's gait," moving his body and swinging his arms at each step. The child cannot skip or jump, and he has difficulty in rising from a chair or in mounting stairs, *which determines the expedient of putting the* hands on the knees, apparently to push the trunk up and to help the extension of the hip joint. If the child is placed on his back on the ground he rises in a fashion which is so peculiar as to be almost pathognomonic of the disease. He first rolls round and assumes a position "on all fours"

(Fig 2) He then extends his knees and bends his head forwards and downwards then keeping his feet fixed he travels backwards on his hands and suddenly transfers first one hand and then the other to his knees (Fig 3) Now he has to extend the hip and he does this by climbing up his thighs Finally he jerks the shoulders back into the erect position with a writhing movement the details of which are hard to fol



Fig 2 Pseudo hypertrophic dystrophy Mode of rising

low In the upright position he leans the trunk backwards to keep the hips extended

Distribution of the Muscle Defects — The defects are greatest in the proximal muscles and diminish distally The hands usually are spared and retain good power till the end the neck and face are spared but enlargement of the masseters has been noted The tongue seldom is affected and never the ocular or laryngeal muscles or the muscles of deglutition

The muscles show a progressive alteration in size and diminution in

power The alteration in size is of two kinds enlargement or atrophy and the enlargement and wasting may be variously distributed so as to give the limbs and trunk an abnormal contour In some cases as the Infant Hercules of Duchenne all the muscles are enlarged on the other hand all the muscles may be wasted with the exception of one group such as the calf muscles or the vasti There is no exact correspondence between the size of the muscles and their power

Enlargement of the Muscles — The muscles commonly enlarged are the



Fig 3 Pseudo-hypertrophic dystrophy Showing mode of rising by climbing up the thighs

bulky muscles the gastrocnemius (Fig 4) and soleus the glutei the infraspinati and supraspinati the triceps and the lower half of the deltoid The vasti may be enlarged or the erector spinæ the anterior tibials are affected less commonly The hand and forearm muscles usually escape but enlargement of the abductor indicis has been reported (J Taylor) and hypertrophy of all the muscles of the thenar eminence The hypertrophied muscles feel firm and hard to the touch

Atrophy of the Muscles — On the other hand other muscles tend to

atrophy from the first especially the latissimus dorsi and the costal portion of the pectoralis major The flexors of the knee the flexors and abductors of the hip and the upper arm muscles often are wasted Diminution in size may precede enlargement but more commonly the muscles

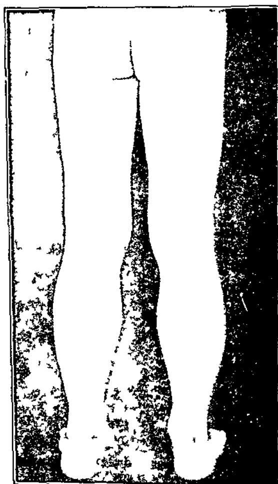


Fig 4 Pseudo hypertrophy of the calf muscles with marked appearance of the overlying skin

which show pseudo hypertrophy later shrink The weakness is less in the stage of hypertrophy than in the stage of atrophy

When a myopathic muscle is put into contraction there may sometimes be observed a cricket ball swelling in the middle of the muscle due to the fact that atrophic changes are most marked at the tendinous

attachments of the muscle These are commonly seen in the quadriceps biceps femoris semitendinous and deltoid (Fig 5)

The weakness of the calf muscles may be demonstrated by the inability of the patient to stand on tiptoe If the dorsiflexor muscles of the ankles are involved he cannot walk on his heels The weakness of the extensors of the knee and the flexors of the hip is easily noted as is that of the extensors of the hip spine and elbows

The atrophy of the costal portion of the pectoralis with persistence of the clavicular portion can be shown by making the patient put the palms of his hands together with his elbows abducted The absence of the latissimus dorsi and lower part of the pectoralis major can be demonstrated by lifting the patient by the axillæ from behind when the scapulæ will be drawn up on the trunk to an abnormal degree



Fig 5 Cricket ball hardenings in the left semitendinosus and right biceps femoris muscles

Defects of Posture and Movement — The distribution of the weakness and wasting gives rise to certain characteristic defects of posture and movement From the weakness of the extensors and flexors of the hip *and the extensors of the knee arises the instability of equilibrium so that* in standing the feet are placed far apart to widen the base The peculiar waddling gait is seen best in cases in which there is weakness of the anterior tibials and the flexors of the hip The feet are widely separated and to clear the ground with the advancing foot the body is inclined to

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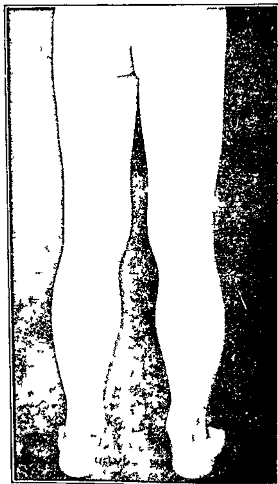


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one side and then to the other the shoulders and the arms are swung so as to bring the centre of gravity of the body well over the foot which is on the ground The gluteus medius in normal walking counteracts this tendency The preponderance of weakness in the extensors of the hip is seen in the great difficulty experienced in mounting stairs

The lumbar lordosis which is accompanied by a compensatory convex curve of the cervical and upper thoracic vertebræ has been shown by Gowers to be due to weakness of the extensors of the hip This weakness causes the forward inclination of the pelvis to be greater in these cases than the normal and since the lowest lumbar vertebræ share the deviation of the sacrum they too become tilted forwards and lordosis appears The compensatory backward inclination of the dorsal spine is necessary to keep the centre of gravity in the normal position and a perpendicular dropped from the centre of the dorsal convexity falls behind the sacrum When the child sits the pelvis rests on the ischial tuberosities, and the forward tilting of the sacrum and lumbar vertebræ disappears and with it the lumbar lordosis If there is weakness of the spinal extensors the back assumes in the sitting position a uniform dorso lumbar curve with the convexity backwards Lateral curvature of the spine is rare and is due to unequal distribution of muscular weakness Weakness of the posterior cervical muscles may cause the head to fall forwards

The positions assumed in rising from the chair or the ground are due to similar causes and are highly characteristic of the disease (Figs 2 and 3)

Contractures — In the later stages where there is disproportionate weakness between flexors and extensors contractures of muscles occur The earliest and commonest is contracture of the calf muscles producing talipes equinus The appearance of this contracture coincides with a diminution in bulk of the calf muscles which probably shrink in length as well as in breadth due to the contraction of the abundant fibrous tissue in the muscle Contractures occur also in the flexor muscles of the elbows and knees in neglected cases and permanent spinal deformities arise in late stages

Fibrillation which is so common a symptom in progressive muscular atrophy is absent in myopathy Rarely muscular twitchings are observed Excitability of the muscles to direct percussion is diminished or abolished contrasting with anterior poliomyelitis where the idiomuscular contractility is exaggerated

Electrical Reactions — The electrical reactions show a diminished excitability of both faradic and galvanic stimulation As the disease progresses and the amount of muscle tissue gradually disappears there

ceases to be a response to either current The reaction of degeneration never occurs

Reflexes — The deep reflexes diminish gradually as the wasting increases The persistence of the knee jerk varies with the activity of the vastus internus part of the quadriceps The superficial reflexes are obtained so long as there are any muscles left to respond to the stimulus Plantar stimulation evokes a flexor response In rare cases an extensor response may be stimulated by an upward movement of the toes on plantar stimulation caused by disproportionate weakness between the extensors and flexors of the toes Rarely in advanced cases there may be dysuria but generally the sphincters are unaffected

Sensation — *Sensibility to all forms of stimulation is unaffected* Subjective sensations of aching and cramp may be referred to the muscles most diseased

Bones — The long bones of the limbs in which the muscle changes are marked undergo atrophic changes These are most marked in the diaphysis The bony protuberances become less marked and rarefaction of the osseous tissue can be demonstrated radiologically The diaphysis is thinner than normal and the meduallary cavity small The length of the bones is unaffected Such bones fracture easily (Marie and Crouzon) Pierre Marie and Onanoff have described a flattening of the occipital region of the cranium which may be due to prolonged dorsal decubitus in early childhood

Cerebral Functions — The cerebral functions are unimpaired and the intellect usually is acute but in some rare cases there has been mental deficiency In a few cases on record there have been epileptic fits

Skin — The mottling or marbled appearance of the skin described by some is probably an exaggeration of that seen frequently in healthy children (Fig 4) The association of the disease with scleroderma has been noted (Ballet and Delherm)

PRIMARY ATROPHIC DYSTROPHY

Ætiology

Inheritance — The facio scapulo humeral type is almost always directly inherited and may be transmitted by males and females Affected members tend to live beyond the age of sexual maturity

Sex — About 50 per cent of children in family groups are affected and in all cases the proportion of males to females is about four males to one female Diehl believes that in many slight cases in adult females

one side and then to the other the shoulders and the arms are swung so as to bring the centre of gravity of the body well over the foot which is on the ground The gluteus medius in normal walking counteracts this tendency The preponderance of weakness in the extensors of the hip is seen in the great difficulty experienced in mounting stairs

The lumbar lordosis which is accompanied by a compensatory convex curve of the cervical and upper thoracic vertebræ has been shown by Gowers to be due to weakness of the extensors of the hip This weakness causes the forward inclination of the pelvis to be greater in these cases than the normal and since the lowest lumbar vertebræ share the deviation of the sacrum they too become tilted forwards and lordosis appears The compensatory backward inclination of the dorsal spine is necessary to keep the centre of gravity in the normal position and a perpendicular dropped from the centre of the dorsal convexity falls behind the sacrum When the child sits the pelvis rests on the ischial tuberosities and the forward tilting of the sacrum and lumbar vertebræ disappears and with it the lumbar lordosis If there is weakness of the spinal extensors the back assumes in the sitting position a uniform dorso lumbar curve with the convexity backwards Lateral curvature of the spine is rare and is due to unequal distribution of muscular weakness Weakness of the posterior cervical muscles may cause the head to fall forwards

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Electrical Reactions — The electrical reactions show a diminished excitability of both faradic and galvanic stimulation As the disease progresses and the amount of muscle tissue gradually disappears there

particularly hereditary which commences in the lower limbs was described by Leyden and by Moebius in 1879

Facio Scapulo Humeral Type — The facio scapulo humeral type begins *usually in infancy and in the muscles of the face* The orbicularis oculi and oris are affected first and then the other facial muscles the zygomatic and the buccinators The eye muscles the muscles of the tongue pharynx and larynx the muscles of articulation and the diaphragm es

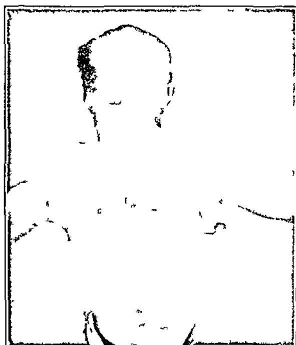


Fig 7 Atrophic dystrophy showing projection of the scapulæ on abduction of the upper limbs

cape The disease spreads to the shoulder girdle the biceps the triceps and supinator longus then to the lower part of the pectoralis major the pectoralis minor the latissimus dorsi the trapezius and the rhomboids Atrophy of the serratus magnus is common The deltoids supraspinati and infraspinati the subscapularis and flexors of the wrist and fingers commonly escape (Figs 6 and 7) Later the disease spreads to the lower limbs affecting the proximal muscles first the flexors of the hip and extensors of the knee and the glutei The muscles below the knee may escape completely

information of the disease is suppressed from reason of vanity and the incidence in females thus may be higher than is believed

Age of Onset — The facio scapulo humeral type has an onset in childhood or adolescence and many cases survive to late life In the juvenile type of Erb onset usually occurs between the ages of 15 and 35 years

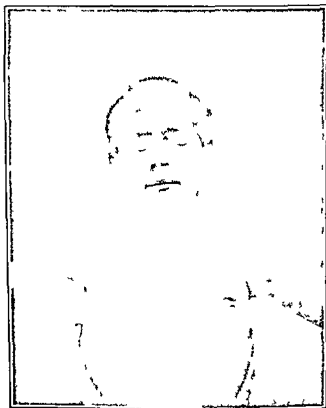


Fig 6 Atrophic dystrophy showing atrophy of the sternal portion of the pectoralis major Note also the projection of the scapulae above shoulders

Symptoms

The types of muscular dystrophy classified under this heading are varieties of one disease and are markedly hereditary The muscles waste from the first and pseudo hypertrophy is absent The *facio scapulo humeral type* described by Landouzy and Dejerine differs only from the *juvenile type* described by Erb in that the facial muscles are affected in addition to those of the shoulder and pelvic girdles A *femoral type*

levator anguli oris and the orbicularis oris are paralysed giving rise to a projection of the lips when the face is in repose The upper lip may project beyond the lower tapir lip (Fig 9) The lips when pressed to



Fig 9 Myopathic facies showing widening of the ocular fissures and projection of the lips tapir lip

gether can be easily forced apart The patient cannot whistle at all or whistles with an inspiratory blast In smiling the buccal fissure is widened transversely There is no withdrawal of the upper lip and raising of the commissures of the mouth as on normal smiling

The Myopathic Facies — The weakness of the facial muscles produces an expressionless countenance and appearance of stupidity which is belied by the patient's intelligent conversation The skin of the face is smooth



Fig 8 Myopathic facies Patient trying to screw up the eyelids

and the forehead unwrinkled The palpebral fissures are wide from weakness of the orbicularis and the eyelids when closed can be easily forced apart (Fig 8) The eyelids may remain slightly apart when the patient blinks or during sleep The naso labial folds are obliterated The

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Body Changes — The shoulders are sloping and thrown forwards from atrophy of the trapezius and the scapulæ winged from weakness of



Fig 10 Atrophic dystrophy showing atrophy of the scapular muscles and loose shoulders

the serratus magnus and the rhomboids (Fig 10) The sternum may be concave and the thoracic wall flattened from atrophy of the intercostals

The clavicles are visible throughout their entire length The arm muscles are wasted and feeble the forearm muscles with the exception of the supinator longus are less affected Landouzy and Dejerine described in two out of their four original cases wasting of the thenar and hypothenar eminences and interossei and this is seen not infrequently The weakness and falling in of the abdominal muscles produces a furrow below the costal margin accentuated when the patient inspires deeply taille en

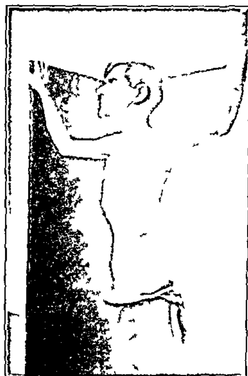


Fig 11 Atrophic dystrophy showing wasp waist deformity

guêpe or wasp waist (Fig 11) The weakness of the thigh muscles produces the same disorder of posture and movement as have been described in the pseudo hypertrophic cases

Juvenile Type —The juvenile type begin about puberty and usually before twenty years Weakness and wasting come on simultaneously first in the biceps triceps and supinator longus The affection is proximal in distribution in the limbs and trunk and the face is not affected The

disease spreads to the muscles of the shoulder and pelvic girdles arms and thighs as in the facio scapulo humeral type The same muscle groups are affected and the atrophy may be slowly progressive over many years and reach an extreme degree Most of the living skeletons in freak shows belong to Erb s group

In both these forms fibrillation is absent and the excitability of the muscles to faradic and galvanic stimulation diminished proportionally to the wasting there is never any reaction of degeneration The deep re flexes diminish gradually as the wasting increases Sensation is never affected Signs of pyramidal disease are absent and the sphincters are unaffected

Femoral Type —The particularly hereditary dystrophy described by

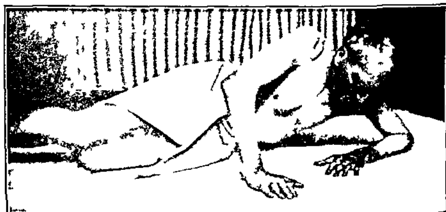


Fig 12 Muscular dystrophy in a man aged sixty years showing difficulty in rising from the ground

Leyden and Mœbius does not differ essentially from the other types of atrophic dystrophy The average age of onset is ten years and there are many cases in the family The disease begins in the hip and thigh muscles and later extends to the shoulder girdle muscles running a slowly progressive course The inheritance seems to be essentially dominant

Sporadic and Late Cases

Isolated cases occur often in one generation only which do not con form to the types described above They are anomalous in their age in cidence in the groups of muscles affected and perhaps in an absence of hereditary or familial characteristics They tend to affect males more fre quently than females They are much more disabling and polymorphic in their manifestations than the more stereotyped dystrophies (Fig 12)

Myopathic dystrophy may be noticed first as late as the age of 60 years (Barnes) In diagnosing such cases of late onset it is important to exclude amyotrophic lateral sclerosis polyneuritis syphilitic amyotrophy fracture dislocations of vertebrae with motor compression signs and acute poliomyelitis Cases occurring in late life tend to be of the simple atrophic type

Trauma and infection are cited frequently as aetiological factors in these cases but they probably act only as factors which determine the onset or accelerate the course of the disease in a patient who is a potential myopathic i e a genotype carrying the mutant gene or genes

Dystrophia Hypertrophica Musculorum

Synonym — Hypertrophia musculorum vera

This rare condition is characterised by excessive muscular development and ultimate enfeeblement of muscular power Males present a Herculean appearance and affected females have an unusually athletic build To palpation the muscles are like those of an athlete in training The hypertrophy may be generalised or limited to one or more limbs The onset usually is in childhood or early life In the earliest stages the patient may be endowed with exceptional strength but this later is inevitably replaced by weakness Barnes's patient at 25 years could climb a flight of stairs with a load of 500 lbs on his back he was a furniture remover and he once wrestled successfully with a performing bear at a circus In the early stages the tendon reflexes may be absent but unless this is so or unless the patient is known to come of dystrophic stock one cannot be certain of the diagnosis until muscular weakness supervenes The power of hypertrophied muscles then diminishes greatly even below that of the normal The weakness may indeed be so great that the sufferer is unable to support the weight of his arms above his head The condition usually is followed by pseudo hypertrophy or atrophy and a patient may exhibit hypertrophy pseudo hypertrophy or atrophy of different muscles at the same time

Distal Dystrophy

Gowers Spiller and others have described an excessively rare distal type of myopathic dystrophy in which wasting of the intrinsic muscles of the hands or feet may occur In the early stages the lower limbs are particularly affected and at first the proximal muscles especially the ileo psoas are more affected than the distal ones The flabby wasted thigh and calf muscles contrast with the well developed muscles of

the shoulder girdles and upper arms Although power is greatly reduced total paralysis does not seem to occur In the first stages wasting of the intrinsic muscles of the hands and the forearms becomes evident with disappearance of corresponding tendon reflexes The condition is distinguished from peroneal muscular atrophy by the absence of sensory changes and fibrillation and by the involvement of the prime movers of the hip joint Sir Thomas Buzzard described an ilio psoas type of dystrophy in a girl of twenty three years who showed also some weakness of the facial muscles

The Dystrophy of Barnes

Stanley Barnes in 1932 described 284 individuals in seven generations of one stock Features of a curious myopathic dystrophy were present amongst the first five generations The average age of onset is between 35 and 50 years Males and females are affected in about equal numbers and inheritance is of the dominant type The disease is transmitted by males and females The first stage is a true muscular hypertrophy associated with abnormal strength and later weakness Pseudo hypertrophy follows usually in middle life and the muscles though enlarged are weak The third stage is terminal and characterised by a spreading atrophy beginning in the large muscles of the thighs and calves and ultimately involving the intrinsic muscles of the hands and forearms The latter groups of muscles waste without antecedent pseudo hypertrophy The disease progresses slowly Loss of tendon reflexes occurs in the first stage and may be the only abnormal sign in some members of the stock There is an almost constant association with adipositas universalis and a relative absence of polymorphism

Diagnosis of Myopathic Dystrophies

The myopathic dystrophies in their typical forms are not difficult to recognise when the condition is clearly hereditary or familial when the onset is in childhood when the disease affects chiefly the pelvic or shoulder girdle muscles and when pseudo hypertrophy is present

In *childhood* the diagnosis must be made from congenital aplasia of muscle Rarely a child is born with absence of the sternal portion of the pectoralis muscle absence of the serratus anterior or absence of the muscles of the abdominal wall These conditions unlike dystrophy are congenital and not progressive The waddling gait and lordosis of bilateral congenital dislocation of the hip joints may simulate pseudo hypertrophic dystrophy but enlargement of muscles is absent and characteristic

telescopic movements of the lower limbs can be produced by traction on the thighs. The *infantile forms* of spinal muscular atrophy usually show in the first year of life, whereas the myopathic dystrophies appear later in childhood. *Peroneal muscular atrophy* can be recognised by the presence of sensory disturbances in the lower limbs with atrophy of typical distribution in the legs and hands. *Acute poliomyelitis* may be proximal and symmetrical in distribution, but there is a history of antecedent febrile illness in such paralyses.

In adult life myopathic dystrophy may be simulated by *poliomyelitis*. *Traumatic palsies* of the serratus anterior or trapezius muscles are met with in young adults and may be bilateral. *Disseminated muscular atrophies* of scattered distribution may follow upon acute infectious diseases, and these may be encountered also in *lead* or *alcoholic neuritis*.

In *hyperthyroidism* and in *Addison's disease* atrophies and diseased muscle states may be met with. In the atrophy of hyperthyroidism tendon reflexes may be diminished or absent.

In the typical case of *progressive muscular atrophy* (motor neurone disease) the disease begins later in life than does a dystrophy, it is not hereditary or familial, and the distal muscles of the limbs are affected first. Fibrillation and true reaction of degeneration occur. Very rarely progressive muscular atrophy may be met with before the age of 30 years, and it should be noted that there is a relatively benign scapulohumeral form, in which the bulbar muscles and intrinsic muscles of the hands are involved late in the disease. The finding of an Argyll Robertson pupil or positive serological tests in the blood or spinal fluid indicate the diagnosis of *syphilitic amyotrophy*. Rapid onset of muscular wasting in an adult should raise the suspicion of *spinal neoplasm* and calls for an examination of the spinal fluid and appropriate roentgenological studies.

Arthritic muscular wasting is accompanied by pain, and deformity or limitation of movement is present in the affected joint or joints.

Radiographic studies of the muscles made with a soft tube may demonstrate enlargement of deep muscles in dystrophy.

In all cases where doubt exists a biopsy of an affected muscle should be made.

Course and Prognosis of Myopathic Dystrophies

Since the myopathic dystrophies tend to show little polymorphism and the type of the disease and its mode of onset remain the same in succeeding generations, a study of the pedigree may provide useful prognostic information.

In sporadic cases the disease is more rapidly disabling and rapid in its progress The earlier the age of onset, the more likely is the disease to terminate in a few years from respiratory complications In male pseudo hypertrophic cases the ability to stand usually is lost at ten to twelve years and death occurs between the ages of fourteen to eighteen years Five sixths of the cases of pseudo hypertrophic dystrophy in males are dead before the age of twenty one years The frequency in childhood of acute fevers especially measles with their associated respiratory complications is an important cause of early death in this group In girls and in cases where the onset is later in life the disease may be more chronic Contractures occur most frequently in the pseudo hypertrophic cases The simple atrophic dystrophies have a later age of onset and run a much slower course They are compatible with fairly long life even with old age Death occurs from intercurrent disease notably pneumonia or pulmonary tuberculosis

Treatment of Myopathic Dystrophies

It is a mistake to keep the patient in bed so long as walking is possible regular daily exercise should be encouraged short of fatigue When muscular exercise is stopped there is a rapid failure of strength Patients who take to wheel chairs or motor cars rapidly lose the power of walking

Massage and friction of the muscles with olive oil improve the circulation and lessen the tendency to contracture Daily active and passive movement of all joints prevents the occurrence of deformities Electricity is a very feeble stimulus to the growth of muscular fibres compared with the physiological stimulus of voluntary effort

Splints used to reduce contractures should be worn only at night and should be made of celluloid Tenotomy may be advised when the contractures are severe enough to prevent the limb being used in its natural position

During the later stages of the disease the patient should be guarded from the pulmonary infections which so frequently end life

As some of the cases show hypoglycæmia Morvan has suggested treatment by injections of serum glucose This substance is a 2½ per cent solution of glucose in normal saline and should be given intramuscularly in doses of 30 c c (one ounce) twice weekly

The administration of aminoacid glycin has been found by some to give rise to definite clinical improvement so long as the glycin is being given The pharmacological effect seems to be largely one of stimulation

of muscular metabolism through the specific dynamic effect of the amino acid Physiologically as a precursor of creatin glycin promotes creatin formation This creatinin may be retained and metabolised by remaining healthy muscle fibrils

The treatment is expensive and large doses of glycin varying from 10 to 30 grams per day are necessary Glutamic acid or monosodium glutamate may be used as substitutes Boiled down gelatine yields 20 per cent glycin and treatment with gelatine in doses of 100 grams per day given by mouth with fruit juice to flavour is worthy of trial The improvement after these treatment usually lasts only from three to four weeks and then gradually disappears The best method of administering glycin is probably to give small doses over period of three weeks with one week s interval between each course reserving large doses for emergencies

Treatment to be effective must be commenced in the early stages of the disease Once the nuclei of the muscle fibres have degenerated no improvement can occur It remains to be seen whether a treatment of this kind is able to avert the inevitable progress of the disease

The treatment of Kure who gives intramuscular injections of 0 2 c c of 1 per cent pilocarpine solution and 0 [illegible] c c of 0 1 per cent adrenalin on alternate days for 50 doses is without scientific basis

MYOTONIA CONGENITA

Synonym — Thomsen s disease

Definition — A rare hereditary and familial muscular disease characterised by delay in initiation of voluntary movement and prolonged tonic contraction and retarded relaxation of the skeletal muscles during and after voluntary movement Prolongation of contraction and delayed relaxation is observed in the muscles on (1) voluntary movement (2) reflex movement (3) direct percussion of the muscle and (4) electrical stimulation of the muscle

An abnormally large musculature with hypertrophy of the muscle fibres often but not invariably accompanies the condition There is little or no progress of symptoms and rarely any improvement

History

The name of Thomsen s disease has been generally adopted since Thomsen a physician of Schleswig Holstein described this malady in 1876 as it affected himself and his four sons K Nissen Thomsen s

In sporadic cases the disease is more rapidly disabling and rapid in its progress The earlier the age of onset the more likely is the disease to terminate in a few years from respiratory complications In male pseudo hypertrophic cases the ability to stand usually is lost at ten to twelve years and death occurs between the ages of fourteen to eighteen years Five sixths of the cases of pseudo hypertrophic dystrophy in males are dead before the age of twenty one years The frequency in childhood of acute fevers especially measles with their associated respiratory complications is an important cause of early death in this group In girls and in cases where the onset is later in life the disease may be more chronic Contractures occur most frequently in the pseudo hypertrophic cases The simple atrophic dystrophies have a later age of onset and run a much slower course They are compatible with fairly long life even with old age Death occurs from intercurrent disease notably pneumonia or pulmonary tuberculosis

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nerve impulse sets free acetylcholin or some analogous substance at the nerve endings and this is destroyed immediately by a cholin esterase normally present in the blood

In myotonic individuals Lanari has produced myotonic phenomena by intra arterial injection of 0 04 gm of acetylcholin while no effect occurs if the acetylcholin is injected into the muscle directly Such an intra arterial injection produces no demonstrable motor effects in normal subjects In sufferers from myotonia the symptoms have been shewn by Ritchie Russell and Steadman to be aggravated by the administration of prostigmin also by the administration of potassium salts Myotonia can be elicited in muscles denervated by local injection of novocain (Schaffer)

While it is probable that the symptom is caused by an abnormality at the myoneural junction the nature of the abnormality is quite unknown It may be the lowering of the threshold to chemical stimuli or absence of destruction of acetylcholin at the myoneural junctions

Myopathic tracings (Schaffer Lindsley and Curnen) show that in both initiation of movement and in relaxation there is a latent period during which greater power must be exerted It is held by some that the muscular hypertrophy is entirely secondary to the myotonia but this is difficult to prove

Symptoms

The patient s first complaint usually is that when he rises from his chair and attempts to walk his legs become bound and rigid in spasm The rigidity may be so marked that he falls like a log After a few seconds during which the muscles relax he is able to proceed With each step that he takes the stiffness becomes less until at last it passes off completely and his gait becomes normal When he grasps an object firmly the contraction continues after voluntary impulses have ceased and his fingers remain for a few seconds tightly clutching the object until his muscles relax If this movement is repeated several times the stiffness passes off and his fingers become supple again A Canadian observer himself a sufferer from the disease has written of how this symptom caused misunderstandings in social intercourse when he had occasion to shake hands with his lady friends

Ballet and Marie s patient while mounting a horse was seized with stiffness in his left leg as soon as he had placed his foot in the stirrup He remained unable to move for a few seconds Then throwing his right leg over the saddle he again became rigid with his leg extended in mid air until the contraction of the muscles passed off

great nephew reinvestigated the pedigree of the Thomsen family and reported examples in five generations

Ætiology

Inheritance — The disease apparently is inherited in the dominant mode Sporadic cases occur In the family described by Rosett the myotonia of the second and third generations was inherited from the female grandparent who was not unduly muscular The excessive muscular development in this family resembled that of the healthy male grandfather Large muscles however do not seem to be an essential feature of the disease In Rosett s family there was a complicating inherited psychosis which is not a part of the usual clinical picture

Sex — The disease affects males far oftener than females Of one hundred and two cases collected by Koch from the literature ninety one occurred in men and only eleven in women

Age — The stiffness usually is complained of at puberty or later but if the patients are questioned carefully a history of symptoms in childhood often can be obtained

Pathology

The lesions are confined to the muscles which may be macroscopically normal Microscopically the myofibrils are increased in size and in number A fibril may measure 60 to 145 micra in diameter i e two to four times the thickness of a normal muscle fibril The sarcolemma nuclei are more numerous than normal and there is an increase in interstitial tissue proportional to the degree of hypertrophy

In the later stages of the malady atrophic fibrils are said to occur amongst the hypertrophied ones On longitudinal section in these late cases certain fibrils may show vacuolation and poor striation recalling the appearances met with in pseudo hypertrophic dystrophy

In several recorded autopsies no abnormality was discovered in the peripheral nerves or central nervous system Unlike myotonia atrophica dystrophic changes elsewhere are completely absent and one does not meet with cataract baldness or testicular or ovarian atrophy in this disease

Pathogenesis

The myotonic phenomena of these diseases probably are due to the abnormality at the myoneural junction In the normal individual the

London complained of diplopia on extreme lateral movement of the eyes which was most marked shortly after waking

In severe cases some residual contraction of the muscles is established so that the aspect of the patient becomes one of general muscular rigidity

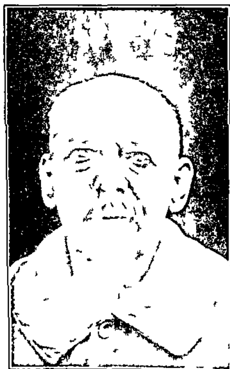


Fig 14 Myotonia on percussion Showing persistent dimpling of the left deltoid some seconds after it has been struck with a reflex hammer

the expression of the face is tense and stiff (Fig 13) and the trunk and limbs lose their mobility

The mechanism of the abnormal muscular action has been studied by Rossett Schaffer and others Myographic tracings show that in both initiation of movement and in relaxation there is a latent period during which greater power must be exerted Complete relaxation may take as long as ninety seconds Thomsen ascribed the disappearance of the

All the voluntary muscles may be affected similarly, or the stiffness may be localised to certain groups i e , it may be localised to the upper or lower limbs alone The jaw muscles go into spasm with the first bite and when the patient has succeeded in chewing the morsel, there may be difficulty in swallowing the bolus When the patient yawns his mouth may remain open for several seconds When the patient laughs the smile remains for a short time fixed on his face When he screws up



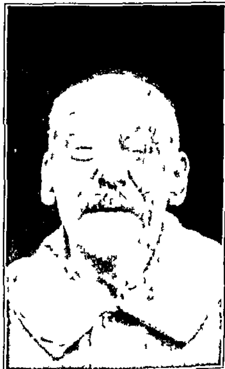


Fig 13 (a) Myotonia showing rigid facies (b) myotonia showing difficulty in opening the eyes when they have been screwed up

his eyes firmly he is unable to open them for several seconds (Fig 13) But after repetition of this movement it becomes easy When he commences to speak his voice is feeble and husky but gradually it increases in strength and clearness When he strains at stool the abdominal muscles become rigid and stiff and when he coughs or sneezes the respiratory muscles contract in expiration and a long period of apnœa follows during which the patient becomes increasingly cyanosed and may even die of asphyxia The external ocular muscles may be affected but usually this is slight One case at the National Hospital, Queen Square

dimple sign. Bechterew has described similar phenomena after kneading the muscles.

The Myotonic Reactions. — The response of the muscles to electrical stimulation are constant and of great value. They were first described by Erb. After a single faradic shock the muscle goes into a state of tetanic contraction which persists for five to thirty seconds after the stimulus has ceased. Galvanic stimulation with a current of even one milliampere may cause muscular contraction and well formed wave like contractions proceeding from cathode to anode may be seen. In this disease K C C and A C C are equally easy to obtain whereas in health K C C is elicited more readily than A C C. The excitability of the nerves to faradism does not seem to be increased and quantitatively the excitability of the nerves to galvanism is normal.

Muscular Hypertrophy. — True muscular hypertrophy is common in members of families affected with this disease. The hypertrophy is general in distribution but is most marked in the calves and muscles of the upper limbs and shoulder girdles (Fig. 15). The patients have a Herculean torso and their strength may or may not be in proportion to the degree of muscular development. The patient may have the appearance of an athlete yet his appearance may be a parody of his powers of performance (Fig. 15). The muscles are firmer to feel than normal muscles and frequently are of a stony hard consistence.

Sensory Phenomena. — Objective sensory changes are absent but patients may complain of aching pains or a feeling like an electric current shooting through the muscles with the onset of a myotonic spasm. The superficial and deep reflexes usually are normal although the latter may be diminished. The sphincters are unaffected and the plantar responses are flexor.

Prognosis

Although intermittent forms of the disease have been described no case of cure is known. The disease does not interfere with the patient living an ordinary active life. It is not progressive until the patient is advanced in years. Death may occur from asphyxia during a myotonic spasm of the respiratory muscles. The general health may be quite unaffected by the disease and longevity is not rare.

Diagnosis

Cases may come under observation because of myotonic symptoms or because of muscular hypertrophy. The disease might become confused

rigidity on repetition of the movement to a concomittant rise in temperature of the active muscle Although usually initiated by attempting voluntary movement the spasms may appear spontaneously The muscular spasm cannot be initiated by passive movements Certain influences especially psychical may initiate the muscular cramp for example the emotion caused by a sudden noise intensifies the spasms as does exposure to cold On the other hand the tendency to stiffness is diminished



Fig 15 (a) Myotonia congenita showing Herculean torso (b) myotonia congenita showing the fingers and arms beginning to droop from weakness

by rest of mind and body by warmth or by the taking of moderate amounts of alcohol as well as by the frequent repetition of a movement

Myotonia on Percussion (*Mechanical Myotonia*) — If the muscle be struck sharply with a hammer it goes into contraction and a dimple appears at the point of impact which may persist for thirty seconds (Fig 14) This is seen best in the muscles of the thenar eminence where a depression appears and the thumb becomes adducted It is also seen well in the tongue where it has been described as Schultz s tongue

entities Myotonia has been observed as an exceptional symptom in myopathic dystrophy one case of Barnes s family showed it in the extensors of the thigh Also it has been seen in syringomyelia Cyclothymia and other mental abnormalities have been described in myotonia congenita but they form no essential feature of the clinical picture

Eulenburg in 1886 under the name *paramyotonia congenita* described a familial affection characterised by tonic spasms of the voluntary muscles especially those of the face which appeared only when the sufferers were exposed to cold There seems to be no reason for regarding it as a separate di ease from myotonia congenita

Of more interest are the cases described as *myotonia acquisita* by Knud Krabbe This observer published a case in 1933 and referred to 35 cases in the literature The condition is said to affect adult males and to have an acute onset after an illness resembling myositis or polyneuritis or after peripheral trauma There is enlargement of the muscles with slowness of relaxation and myotonic electrical responses and a tendency to improve No family history was ascertained in these cases and the condition seemed to be acquired in adult life In Krabbe s case biopsy of the muscles showed no abnormal signs The syndrome seems to be distinct from tetany and possibly is due to some transient local chemical change in the muscles

Myxœdema with Myotonia and Muscular Hypertrophy — Weitz has described a case of post operative myxœdema in a man aged 44 years associated with increased tonicity of the muscles and painful cramps on sudden voluntary movements Myotonia on percussion was present In Garcin s case hypertrophy of the muscles was present also possibly secondary to the myotonia

It is exceedingly difficult to separate such cases from tetany and in Weitz s case hyperexcitability of the nerves as well as the muscles was present It is important to note however that in Garcin s case *thyroid* not para thyroid medication led to a disappearance of the symptoms

Myotonia Atrophica

Synonym — Dystrophia myotonica See Chapt XIV Vol VI

II MYELOPATHIC DYSTROPHIES

In the infantile forms of spinal muscular atrophy in peroneal muscular atrophy and in progressive hypertrophic polyneuritis simple atrophy of the muscles of characteristic distribution is accompanied by degenerative

with myotonia atrophica dystrophia myotonica but in that disease muscular atrophy especially of the sterno mastoid is present constantly there is characteristic weakness of the facial muscles and dystrophic symptoms especially cataract are present

In tetany the disease is not familial or hereditary and the attitude of the hands and feet in the attacks usually is characteristic Moreover, the myospasms are initiated by pressure or percussion of the peripheral nerves and by occluding the main artery to a limb

In tetany myotonic electrical reactions are absent The rigidity of tetanus is constant though subject to exacerbations and percussion myotonia is not observed in that disease

Forced grasping observed in destructive lesions of the premotor cortex has to be distinguished from myotonia Forced grasping is a tonic perseveration of the flexor muscles of the fingers following scratching or touching the palm Walshe and Robertson have pointed out that the adequate stimulus for the elicitation of the grasp is stretching of the flexor muscles of the fingers In such cases other symptoms of the cerebral lesion are present e g inability to perform fine finger movements increased tendon reflexes extensor response and vasomotor disturbances in the affected limbs Myotonia has to be distinguished also from the inability to relax which occurs in athetosis

Treatment

Patients should lead an active life in so far as their disease permits and should be protected from cold which aggravates the myotonia Wolf Russell and Stedman and Foster Kennedy report that myotonic phenomena can be abolished within ten minutes after intravenous administration of 0 6 gm (gr x) of quinine bihydrochloride intravenously The effect lasts fifteen to twenty hours The writer has been unable to confirm this with myographic tracings Kennedy states that the spasms can be diminished by regular quinine administration by mouth and gives 0 3 gm (gr v) of quinine bihydrochloride by mouth two or three times a day or in colder weather 0 6 gm (gr x) Thyroid atropin posterior pituitary calcium chloride and calcium gluconate have been tried also Moderate amounts of alcohol are beneficial

Aberrant Forms of Myotonia

The two chief diseases in which myotonia occurs viz myotonia congenita and myotonia atrophica dystrophia myotonia are clear cut clinical

be observed to break up into many small fibrils Vacuolation and fatty infiltration are absent

Owing to the tendency of amyotonia congenita to spontaneous recovery our knowledge of the cord changes is scanty Only a few cases have come to autopsy a considerable number of cases of Werdnig Hoffmann disease have been published with pathological findings

Grinker in a review of the pathology of the two diseases points out that in amyotonia congenita the ventral horns show simply a falling out of the ganglion cells without reactive changes In the Werdnig Hoffmann disease the ventral horn cells show signs of active degeneration there is neuronophagia and proliferation of glial cells One may conclude that in amyotonia congenita the morbid process is stationary and at an end in the Werdnig Hoffmann disease it has commenced later in life and is active

AMYOTONIA CONGENITA

Synonyms — Oppenheim s disease myotonia congenita (Oppenheim) infantile type of myopathy (Batten) congenital amyoplasia

Definition — A prenatal or congenital malady sometimes familial commencing in intrauterine life characterised by (1) extreme symmetrical atonia of the limbs and trunk (2) weakness and smallness of muscles and (3) diminution or loss of the tendon reflexes in the early stages The cases show a tendency to improvement and partial recovery

History

In 1900 Oppenheim first described this disease under the name myatonia congenita Spiller in 1905 made a pathological investigation on a case aged 22 months and found no spinal cord changes Collier and Wilson in 1907 reported another case and gave the condition the name amyotonia congenita which is the least confusing of all the suggested titles

Slauck and later Krabbe in 1920 pointed out the similarity to the Werdnig Hoffmann disease In 1927 Greenfield and Stern confirmed the anatomical identity of the two diseases R R Grinker in 1927 reviewed the pathological findings in the two conditions

Ætiology

Inheritance — Amyotonia congenita is less frequently familial than the Werdnig Hoffman disease but familial cases are met with The disease does not seem to occur in successive generations

changes in the ventral horn cells of the spinal cord or in the peripheral nerves These diseases are termed myelopathic dystrophies

THE INFANTILE FORMS OF MUSCULAR ATROPHY

Amyotonia congenita Oppenheim s disease and the progressive spinal muscular atrophy of infants the Werdnig Hoffmann disease constitute the infantile forms of muscular atrophy

They differ from the dystrophies hitherto described in that they are congenital i e manifest at birth or become evident during the first year of life Clinically the affected infants suffer from a symmetrical extreme flaccidity of the limbs and trunk which allows of the child being placed in grotesque attitudes of hyperextension and hyperflexion without pain The muscular atrophy is not very marked or is made out with difficulty under the diffuse subcutaneous fat of the infant Clinically the diseases tend to be confused not so much with the other dystrophies as with diseases which cause retardation in walking and physical development e g rickets syphilitic epiphysitis encephalopathies and cerebral diplegia

The main clinical differences between the infantile forms of muscular dystrophy may be tabulated as shown in Table I

TABLE I

	AMYOTONIA CONGENITA *Oppenheim s disease*	THE WERDNIG HOFFMANN DISEASE
Inheritance	Not markedly inherited or familial	Marked familial incidence some times hereditary
First manifest	Evident in intra uterine life or at birth	Evident between 8th and 1 th month of extra uterine life
Muscular atrophy	Diffuse smallness of muscles under the subcutaneous fat of infancy	Localised atrophy may be present e g in the pelvic girdle muscles
Nutrition	Well nourished infant	Cachectic infant
Clinical course	Tends to partial recovery	Tends to complete paralysis and death within 4 or 5 days

Pathologically the changes are confined in both conditions to the lower motor neurone and the muscles In both diseases the muscle changes are identical Histological sections show muscle fibres in miniature with normal striations Here and there a fibre of normal size may

be observed to break up into many small fibrils Vacuolation and fatty infiltration are absent

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Ætiology

Inheritance —Amyotonia congenita is less frequently familial than the Werdnig Hoffman disease but familial cases are met with The disease does not seem to occur in successive generations

Age of Onset — In a large number of cases the peculiar flaccidity and weakness of the muscles has been noticed so soon after birth as to make it certain that the disease was congenital The story given by the mother is often that during pregnancy quickening was absent but it must be remembered that quickening is a notoriously irregular phenomenon The pathological findings in the anterior horn cells speak for an onset in intrauterine life

Sex — The sexes are affected alike

Infection — In three cases noticed soon after birth recorded by Collier and Wilson the disease followed on an acute febrile illness Such acute fevers however probably only tend to call attention to a condition which is congenitally installed There is no pathological evidence that the disease is due to intrauterine poliomyelitis as Marburg has suggested

Pathology

The ventral horn cells are diminished in number and those remaining show atrophy chromatolysis or malformation Some are hypertrophic The cells of the lateral and posterior horns are intact There is a striking absence of glial reaction suggesting that the pathological process is completed or stationary Motor cranial nerve nuclei may show similar diminution in the number of ganglion cells

The muscles show a simple atrophy and there are large numbers of very small clearly defined muscle fibrils Larger fibrils seem to split up into smaller ones Forbus believes that the small myofibrils are embryonic and have never received a nerve supply He regards the disease as a nonprogressive defect of development of the ventral horn cells of the spinal cord There is no increase of fat or connective tissue in the muscles The vessels show thickening of their walls The diaphragm tends to escape or is affected sparingly The heart muscle is of the fœtal type and its fibres are thin and poorly developed

Symptoms

The muscles are extremely flaccid toneless and weak Muscular atrophy is difficult to make out underneath the thick subcutaneous fat when the patient is an infant In later life it is more evident There may be complete paralysis at some but not all of the joints When paralysis exists it is usually of the lower limbs The child is small for its age and growth generally may be a little retarded Mentally the child is bright and intelligent

If the child is placed in the sitting position the body bunches up the head tends to loll forwards on the chest The thorax is small and the belly projects If the intercostals are affected the breathing usually is diaphragmatic Although the limbs can be moved spontaneously they frequently cannot be raised against the action of gravity The child is



Fig 16 Amyotonia congenita showing grotesque posture allowed by the atonic musculature

unable to maintain the sitting position without the support of pillows The extreme flaccidity of the limbs allows of their being placed in grotesque positions without discomfort to the patient (Fig 16 and 17) Thus the heels may be placed in contact with the occiput the dorsal aspect of the fingers in contact with the extensor surface of the forearm the ankles may be dorsiflexed until the great toes touch the tibiae The relaxation of the muscles and ligaments is such that the arms can be passively shaken like a flail and the joint surfaces of the knees and

elbows may be separated The general contour of the limbs is only altered in so far as the muscle eminences are less distinct than normal

The foot is characteristic (Fig 18) It is long and narrow and tends to be everted The sole is rounded transversely soft and padlike, and lacks the normal skin furrows Pads of fat tend to occur on the dorsum of the feet On palpation a soft velvety sensation is imparted to the

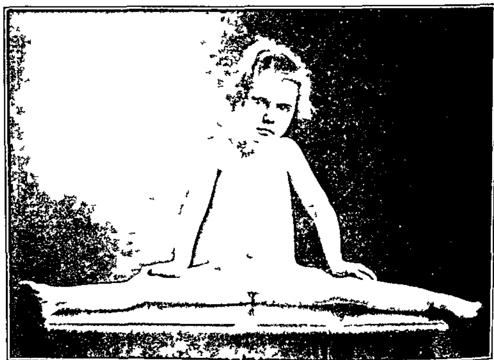


Fig 17 Amyotonia congenita showing atonia of the muscles of the thighs

touch and it may be impossible to distinguish between skin, subcutaneous tissues and the underlying muscles when the muscles are put into contraction The os calcis projects markedly backwards beyond the line of the tendo Achillis The hands are long soft and narrow

Muscles — There is no local wasting of muscles and atrophy of individual muscles never occurs The smallness as a rule tends to be more marked in the distal muscles and the lower extremities are more affected than the upper Everywhere the muscles are soft and although loss of power is marked complicated movements can be performed with an amazing degree of speed and precision if the effect of gravity is overcome by supporting the limb Fibrillation is absent The facies may be somewhat expressionless and dull looking owing to hypotonia of the

facial muscles but there is rarely any weakness and never wasting of the facial muscles The diaphragm seldom is involved When the intercostals are affected the lower interspaces are retracted during inspiration coughing and crying are feeble and there may be cyanosis as a result of this muscular weakness

Contractures — Notwithstanding the flaccidity moderate contractures of the hamstrings the tendo Achillis adductors of the thigh flexors of

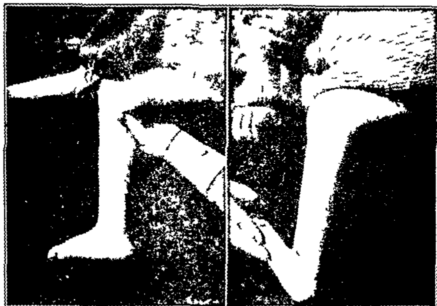


Fig 18 (a) Foot in amyotonia congenita showing projection of os calcis and roundness of the sole (b) amyotonia congenita showing atonia of calf muscles

the elbow or sternomastoids are present in most cases Deformities of the chest and spinal curvature arise as a result of defective muscle tonus

Atonia — The atonia like the smallness of muscles always is strictly symmetrical in the limbs and trunk and is most marked in those regions where the smallness of muscles is most conspicuous

Reflexes — The superficial reflexes are normal The deep reflexes invariably are diminished or absent but they may return as the patient improves with advancing years The sphincters are never affected in amyotonia congenita

Electrical Reactions — The faradic irritability of the muscles is

diminished or lost A delayed response to faradism with normal galvanic responses is so characteristic of amyotonia that to it the name of amyotonic reaction has been applied A remarkable symptom is that the strongest faradic stimulation can be borne without pain

Sensibility — Sensibility apparently is normal notwithstanding the tolerance of these patients to strong faradism In no case has definite loss of pain sensibility to pin prick been demonstrated The high faradic tolerance probably is connected with the atonic condition of the muscles and not with changes in the nerves

Nutrition — Bassoe has pointed out that in most cases unlike the Werdnig Hoffmann disease nutrition is well maintained and the children seldom appear ill or cachetic

Diagnosis

The diagnosis is made on the appearance at birth or within the first year of life of strictly symmetrical flaccidity weakness without complete paralysis and loss of the deep reflexes Cerebro cerebellar atonic types of cerebral diplegia are distinguished by the presence of tendon reflexes and normal electrical reactions Muscle removed by biopsy is normal in appearance In atonic diplegia when the child is suspended by the shoulders the lower limbs become flexed at the hip and knees and rigid although quite flaccid in other conditions In atrophic dystrophy the characteristic muscular flaccidity is absent there is local muscular wasting the symptoms are never apparent at birth and the disease tends to be progressive Conditions of rickety weakness and syphilitic pseudo paresis are never associated with loss of the tendon reflexes Obstetrical injuries causing a flaccid quadriplegia from fracture dislocation of the cervical vertebræ and cord compression show a characteristic deformity of the vertebræ and retention of urine in the stage of spinal shock In such cases there is local paralysis and almost always a history of breech delivery Diphtheritic polyneuritis is very rare during the first few years of life and is associated with a characteristic history and nasal regurgitation of fluids Children during the first year of life seem almost immune to acute poliomyelitis and the absence of a history of pyrexial onset serves to make the diagnosis In the Werdnig Hoffmann disease familial progressive spinal muscular atrophy the disease appears between the eighth and twelfth months of extrauterine life localised atrophy occurs and may be seen in the pelvic girdle the paralysis is more complete and the infant tends to be ill and cachetic The disease never is present at birth and it tends to be progressive

Course and Prognosis

The severe cases die of intercurrent respiratory disease or myocardial insufficiency in the early stages of the malady but the general tendency of the disease is to spontaneous improvement over a number of years The atonia lessens the muscles gradually begin to develop substance and shape the reflexes commence to return and the child becomes able to sit up at the age of four to five years The patient ceases to be bedridden and begins to crawl or moves in the sitting position by pressing the outside of the feet on the floor and drawing the body towards them with a jerking movement Usually between the ages of five and ten years the child learns to walk

In later life these patients may be able to follow some useful occupation although some weakness smallness and hypotonia of the muscles remain They may walk well but cannot run and have difficulty in climbing stairs The persistence of smallness and weakness of unused muscles may lead to an appearance in later life very suggestive of atrophic dystrophy There is no recorded instance of complete recovery Spinal curvature deformity of the chest and feet may develop in untreated cases

Treatment

The natural tendency of the disease to improve may be aided by special measures which have for their object the improvement of muscular nutrition Regular massage and passive movements are of value Every encouragement should be given the child to use the feeble limbs as much as possible and movements may be taught in a bath where the limbs are least encumbered by gravity The employment of splints or heavy mechanical supports is to be deprecated for they prevent that freedom of movement which is essential to improvement If splints are necessary to correct deformities they should be of celluloid and worn only at night Contractures should be treated by daily stretching and corrective manipulation where they are of such degree as to prevent the limb being used normally tenotomy is indicated

General tonics such as iron strychnine and cod liver oil will improve the general condition bronchial and intestinal infections should be guarded against

WERDNIG-HOFFMANN DISEASE

See Chapt XIV Vol VI

Peroneal Muscular Atrophy

Synonyms — Charcot Marie Tooth type of muscular atrophy neuritic type of muscular atrophy

Definition — An hereditary and familial disease of early life characterised by localised paresis with a progressive muscular wasting of the distal muscles of the limbs *The wasting is at first prominent in the* peroneal group of muscles and later in the intrinsic muscles of the feet and hands It usually fails to advance above the lower thirds of the thighs and the upper arms The wasting is accompanied by characteristic deformities e g claw foot loss of tendon reflexes fibrillary tremors and vasomotor disturbances in the affected parts Sensory disturbances are present commonly slight defects of deep sensibility The face trunk and proximal muscles escape and about the third decade of life the disease ceases to progress Anatomically definite changes in the spinal cord have been established

History

Charcot and Marie in February 1886 described this disease in a paper which they illustrated with five personal cases Later in the same year Howard Tooth in his Cambridge thesis independently described the same condition to which he applied the name the peroneal type of progressive muscular atrophy

Prior to that year cases of peroneal muscular atrophy had been described but were classified with the progressive muscular atrophy of Aran Duchenne Virchow had published a case in 1855 M Eulenburg described peroneal muscular atrophy in twins in 1856 and stated that he had read of no similar case before

In 1873 Eichorst had published an account of the affection in thirteen members of six generations and in 1880 Osler described the disease in thirteen cases of two generations in the Farr family of Vermont These writers however unlike Charcot Marie and Tooth failed to separate the clinical picture from that of progressive muscular atrophy although *Osler in 1895 when he was familiar with* peroneal atrophy *refers to the* example of this disease in the Farr pedigree which he had published fifteen years before Julia Bell has given a masterly account of the peroneal type muscular atrophy with an analysis of 96 pedigrees Her volume includes the remarkable family described by Findlay of Aberdeen with 7 generations involved and a family described by herself and H W Armstead with 5 generations

Ætiology

Inheritance — The disease is hereditary and Julia Bell has pointed out that inheritance may occur in all the modes She divides the cases into three groups (a) those who have one parent affected and conform to the dominant type of inheritance (b) those cases who have both parents normal and may be examples of the recessive type of inheritance (c) cases which illustrate sex linked inheritance The disease may skip a generation and then reappear

In some families it is sometimes possible to predict which of the children will develop the disease subsequently by ascertaining their curious inability to taste phenyl thiocarbamide (R A Fisher) This is a bitter substance which is present in the rind of grapefruit

Sex — Males are affected five times as frequently as females Herringham has recorded a family in which the disease was sex linked affecting the males only and transmitted by the unaffected females The potentiality to transmit the disease however is commonly similar in both cases

Age of Onset — The age of onset seems to fall most commonly between the ages of 5 and 15 years In 60 per cent of cases where the inheritance is in the recessive mode the age of onset is before the age of 9 years but cases are recorded where the onset seems to have been as late as the fortieth year Where one parent only is affected about half the children exhibit a striking tendency to develop the disease at the same age as did the affected parent This fact is of some importance as parents want a guide to the age at which they may rest content that their children will not develop the disease they have learned to dread

Trauma or Acute Infections — These probably act by first calling attention to the presence of disease which is congenitally installed but not manifest until later life

Pathology

Most of the cases which have come to autopsy are advanced cases of the disease and it is not at present possible to state definitely if the primary lesion is in the peripheral nerves or the spinal cord The changes in the muscles are secondary there is simple atrophy of the muscle fibrils which shrink stain deeply and later lose their striation In advanced cases the fibres become largely replaced by connective tissue The peripheral nerves may show some degree of interstitial neuritis particularly in the terminal motor branches but in Sainton s case the

larger nerves such as the sciatic were normal The *ventral horn cells* in the cervicodorsal and lumbosacral regions show atrophy with atrophy of the corresponding ventral roots Degenerations of the posterior columns (Fig 19) especially in the tract of Burdach, is found most extensively in the highest parts of the cord (Dejerine) Slight degenerations have been described in the pyramidal tracts and in the cells of Clarke s column In this connection it may be remembered that Biemond

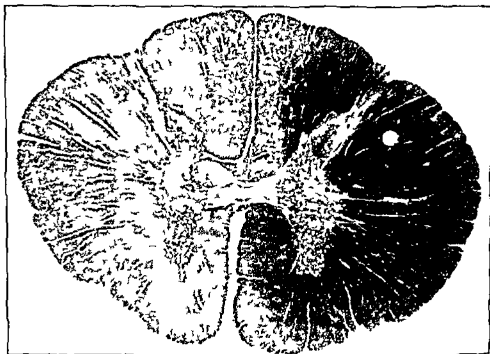


Fig 19 Transverse section of th cervical cord in peroneal muscular atrophy showing degeneration (white stippling) in the columns of Goll

has described cases of peroneal atrophy in a family in which the typical disease was replaced occasionally by a *spinal cord condition* resembling hereditary ataxia

Symptoms

Mode of Onset — In the great majority of cases the disease commences first in the legs and feet In rare instances the disease has commenced in the hands or all four limbs have been affected simultaneously It is uncommon for the disease to be confined to the lower limbs but the

spread to the hand and forearm muscles may take as long as forty years after the onset in the legs Cases have been published where the disease was unilateral but characteristically the disease is bilateral and symmetrical in distribution The first symptom may be increasing weakness

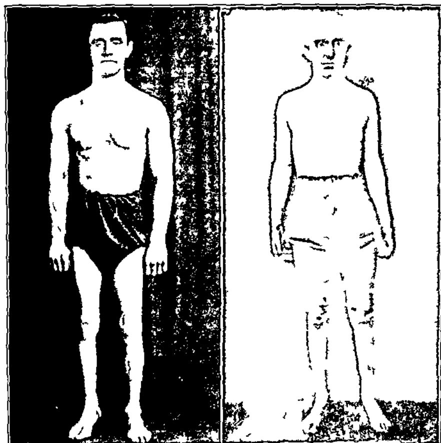


Fig 20 (a) Peroneal atrophy affecting only lower extremities (b) peroneal atrophy affecting hands and lower extremities

and wasting of the legs change in the gait deformity appearing in the feet or inability to move the great toe

Muscular Atrophy — A gradual atrophy begins in the feet in the interossei and plantar muscles The instep becomes hollowed and the foot thin Atrophy and weakness spread to the peronei the extensor longus hallucis and extensor communis digitorum muscles and the feet and toes

larger nerves such as the sciatic were normal The ventral horn cells in the cervicodorsal and lumbosacral regions show atrophy with atrophy of the corresponding ventral roots Degenerations of the posterior columns (Fig 10) especially in the tract of Burdach, is found most extensively in the highest parts of the cord (Dejerine) Slight degenerations have been described in the pyramidal tracts and in the cells of Clarke s column In this connection it may be remembered that Biemond

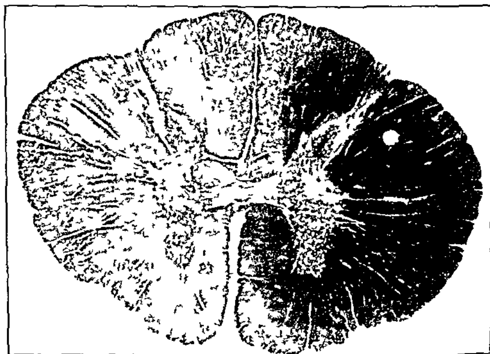


Fig 10 Transverse section of th cervical cord in peroneal muscular atrophy showing degeneration (white stippling) in the columns of Goll

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Fibrillation — This is rarely if ever absent during the periods of activity of the disease although it is never extensive or generalised Fibrillation disappears temporarily during periods of quiescence of the disease and completely when the disease has become arrested Myotatic irritability is increased at first and then diminished in the affected muscles

Sensory Changes — At the onset subjective cramps and aching and tingling may be present in the affected muscles but the disease commonly is painless Gross sensory loss is rare and tactile sensibility is impaired only on the soles of the feet or in the regions of greatest muscular wasting Commonly there is impairment of osseous sensibility to vibration or of postural sensibility in the feet or hands rarely there may be complete loss of all forms of sensation below the knee The muscles and nerve trunks are not tender

Reflexes — The tendon reflexes are diminished or lost in proportion to the wasting The ankle jerks are absent in the later stages while the knee jerks remain active as the vastus internus is unaffected by the disease The superficial reflexes are brisk The plantar responses often are lost at the toes and this is not surprising in a disease where loss of voluntary dorsiflexion of the great toe is an early symptom The sphincters are intact

Deformities and Vasomotor Changes – The same type of deformity tends to be repeated in an affected family Pes cavus a varus deformity with callosities on the outer border of the foot subluxation of the astragalus broad short feet with clawed toe and flat flail feet all are described In the hands the deformity produced is either a flat simian hand with deep interosseous clefts or else a claw hand with hyperextension of the metacarpophalangeal joints and flexion of the interphalangeal joints The feet are cold flushed or bluish and often are covered with abundant sweat Striation of the nails is seen Callosities may occur on the soles of thin deformed feet and these may break down to form perforating ulcers where loss of sensibility is great The vasomotor symptoms probably are due to an associated degeneration of the autonomic nerves which accompany the peripheral spinal nerves

Associated Defects — In the family reported by Biemond a spinal cord disease resembling hereditary ataxia replaced the peroneal atrophy in certain affected individuals Cases of peroneal atrophy with myopathic dystrophic symptoms myopathic facies atrophy of shoulder and pelvic girdle muscles have been described Mental defect optic atrophy and extension of the muscular atrophy beyond the usual limits of the disease may occur rarely and when they do such conflicting symptoms

become dropped and claw like with a tendency to inversion. Inability to move the big toe and loss of dorsiflexion of the feet and abduction are early signs. Wasting is next seen in the anterior tibial muscles and gastrocnemii (Fig. 20). Tooth in his original description stated that the intrinsic muscles of the feet were never the first to be attacked and that the disease commenced most often in the peronei.

The muscular atrophy, as Charcot pointed out, progresses from the distal to the proximal extremities of the muscles. In the lower limbs the atrophy progresses upwards inch by inch until the lower third of the thigh is reached, and there it ceases. The extensors of the thigh are not affected above this level, and the vastus internus may escape. The appearance of well developed upper thigh muscles with complete atrophy of the muscles round the knee joint and below the knee has been compared to an inverted champagne bottle. French clinicians have termed it "atrophie en jarretière" or "jambe de coq". Later a similar atrophy commences in the intrinsic muscles of the hands (Fig. 20). The thenar and hypothenar eminences flatten with wasting of the interossei and short abductor of the thumb. Later the wasting extends as high as the elbow joint, where it stops. It is sometimes stated that the supinator longus escapes, but this has not been so in cases observed by myself. It is rare to see any severe limitation of movement at the wrists, but frequently there is inability to extend the fingers at the interphalangeal joints. Movements at the elbow joint are perfectly free.

The shoulder and pelvic girdle muscles are unaffected and may show a strong development. Atypical cases are described where they have been affected, or where there has been coincident affection of the facial muscles (myopathic facies) or muscles of mastication.

It is important to realise that the muscular wasting may not be symmetrical in its distribution. One lower extremity may be quite normal, the muscles of normal size and consistency, the power good and the reflexes normal, while the other shows the characteristic disease changes.

The affected muscles show diminished electrical excitability corresponding to the degree of atrophy. The completely atrophied muscles may show the reaction of degeneration, but this is not always found even in the most advanced cases. The peripheral nerves may show diminished excitability to electrical stimuli, both faradic and galvanic.

Gait. — The lower limbs are affected more severely than the upper. Early loss of dorsiflexion of the toes and feet with inversion and dropping of the feet leads to a "high stepping gait". Shuffling and slight ataxia are met with also. In the fully developed disease most patients have difficulty in pulling themselves upstairs or walking even on the level.

tends to be associated with tenderness of the muscles and more marked sensory disturbances In cases of progressive hypertrophic polyneuritis the superficial nerves are thickened and hardened

Treatment

Treatment does not have any effect on the course of this disease The nutrition of the affected muscles should be maintained by massage and passive movements Light celluloid splints may be worn at night to correct deformities of the feet and hands Such deformities when established should be treated by manipulation and the wearing of light orthopedic apparatus rather than by tenotomy Arthrodesis of the ankle joint may be performed with benefit in cases with drop foot

All unnecessary fatigue should be avoided and the walking boots should be light and lacing high The use of any heavy mechanical support is to be deprecated Regular exercise short of fatigue should be prescribed to improve the patient s general health Prolonged rest or taking to a wheel chair may result in loss of the ability to walk

FAMILIAL CLAW FOOT

Symonds and Shaw have described an abortive form of peroneal atrophy in which the presenting symptom is claw foot It appeared in members of three generations of a family comprising 36 individuals Most of the cases showed an absence of ankle jerks or impairment of other tendon reflexes and some had wasting of the intrinsic hand muscles

PROGRESSIVE HYPERTROPHIC POLYNEURITIS

Synonym — Hypertrophic interstitial polyneuritis

Definition — A rare disease sometimes familial showing only two constant features (1) a peculiar and sometimes marked enlargement and sclerotic hardening of the peripheral nerves and (2) peripheral muscular atrophy commencing in the feet and hands (See Vol V Chapt XLIII–A for additional discussion of this disease)

History

Dejerine and Sottas with whose names the disease usually is associated reported two cases in 1893 Their patients were a woman of 45 years who came to autopsy and her affected younger brother aged 33

tend to be reproduced in other members of the same stock Other asso ciated defects which have been described are scoliosis unequal pupils external ophthalmoplegia nystagmus deafness epilepsy and perforating ulcers

Course and Prognosis

The disease is not incompatible with a long life of activity Cases are recorded who had the disease for over 70 years The extra effort conse quent on the muscular weakness probably slightly shortens life A patient of E J Adrian was able to pursue his work as an omnibus conduc tor throughout his disease and a case of my own in which there was marked wasting of the hand muscles achieved considerable distinction as an oarsman The disease progresses slowly and irregularly and its course may be influenced adversely by intercurrent disease Final arrest may occur at any stage of the illness but most commonly in the third decade There is never any tendency to recovery of the affected muscles but the patient learns to overcome his defects Increase of intramuscular fibrous tissue may actually lessen the disability by giving support to the joints With modern orthopædic treatment deformities need never arise

Diagnosis

The diagnosis is based on (1) the appearance in childhood or in young adult life of wasting of muscles of the typical distribution with preserva tion of the proximal muscles and the muscles of the trunk and face (2) the presence of vasomotor disturbances and sensory loss in some cases (3) fibrillation in the affected muscles and (4) the existence of the same disease in other members of the family

In progressive muscular atrophy the wasting is never so closely con fined in its distribution as it is in this disease and sooner or later the wasting becomes generalised Peroneal muscular atrophy is hereditary and usually commences in childhood whereas it is rare for progressive muscular atrophy to commence in childhood The usual types of myop athy are distinguished by the incidence of the wasting upon the muscles of the shoulder and pelvic girdles and the face and the absence of fibril lation

Dystrophia myotonica involves the facial muscles this and the atrophic sternomastoids and the presence of myotonic and dystrophic symptoms separate it from peroneal muscular atrophy The onset of multiple neuritis is more rapid than the slow march of this disease and it

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years Two other brothers in the family were unaffected In 1889 Gombault and Mallet had previously described the condition Dide and Courjon published five cases in 1919 but there was no biopsy or autopsy on any of them

De Bruyn and Stern reported 12 cases verified histologically and gave case records of 14 cases in 1929 and in 1930 Ritchie Russell and Garland described 7 cases in four generations of the same family performing biopsy of the internal cutaneous nerve of the left arm in two of these cases

Ætiology

Sporadic cases occur but the disease usually is familial and may be hereditary affecting males and females The first onset of symptoms may be in childhood but in the cases of De Bruyn and Stern Harris and Newcombe and Long the onset was in adult life The reactive changes in the peripheral nerves probably are secondary to a change which is primarily degenerative

Bielschowsky believes the condition to be a diffuse plexiform neuroma of the spinal peripheral nerves He pointed out the similarity of the condition to neurofibromatosis

Pathology

The peripheral nerves ganglia and spinal nerves are thickened and sclerotic and the nerves may present a beaded appearance Microscopically the thickening is seen to be due chiefly to hypertrophy and proliferation of the cells of the neurilemmal sheath of Schwann which coalesce into homogeneous masses or become flattened into layers like the imbrications of an onion bulb The myelin sheaths of the nerves and the axis cylinders degenerate peripherally The perineurium is thicker than normal and nerve fibres are separated from one another by dense envelopes of fibrous tissue derived from the endoneurium Sensory as well as motor fibres degenerate and in the spinal cord degeneration possibly secondary of the posterior columns of Goll is frequently but not invariably present This is best looked for in the lumbosacral regions The posterior root ganglia show degenerative changes Atrophy of ventral horn cells may be noted The muscles show the changes of simple atrophy

Not only the nerves of the limbs but the cranial nerves the spinal roots and the roots of the cauda equina may be affected The autonomic nerves may be involved also

Symptoms

Hypertrophy of Nerves — The peripheral nerves are palpably enlarged and hardened This can be demonstrated clinically in the superficial parts of the ulnar nerve the superficial branches of the musculospiral the internal cutaneous nerve of the forearm and in the peroneal nerve in the leg If the patient be asked to rotate his head laterally hypertrophied transverse and ascending muscles of the superficial cervical plexus can be seen and felt The hypertrophied nerves may appear beaded to the touch

Muscular Atrophy — Muscular weakness and wasting develop symmetrically and peripherally in the limbs as in polyneuritis The hands or the feet may be affected first or all four limbs simultaneously but the symptoms usually are most marked in the lower limbs where the atrophy spreads upwards to the lower parts of the thighs Difficulty in walking often is an early symptom Fibrillation may be present in the affected muscles In the later stages kyphoscoliosis claw hand and claw foot may occur but pes cavus may be present as a congenital defect rather than as a result of this disease

Involvement of the sensory roots and nerves leads to lightning pains and stocking and glove cutaneous sensory impairment loss of postural sensibility leads to sensory ataxia and the gait and symptoms generally resemble those of tabes dorsalis Where sensory changes are profound perforating ulcers may be present Arthropathies have been described with progressive hypertrophic polyneuritis

The tendon reflexes are diminished or lost in the affected muscles the plantar responses commonly are absent at the toes there is no sphincter disturbance The pupils often are small and react sluggishly to light this probably is due to involvement of the cervical sympathetic fibres in the first thoracic roots Dejerine and Sottas described the finding of an Argyll Robertson pupil in their second case but their patient had acquired syphilis at the age of 24 years so that this finding may be discounted

Nystagmus frequently is present Boveri described a family with associated exophthalmos Unilateral papillœdema has been observed presumably due to extension of the pathological process to the optic nerve Nerve deafness may be present Intention tremor and scanning speech were noted in Marie and Boveri s case In the case of De Bruyn and Stern diarrhœa and achylia gastrica were present Pierre Marie also described a case with persistent diarrhœa The spinal fluid may show an increase of protein

Diagnosis

The disease is distinguished from tabes dorsalis, syphilitic amyotrophy and slowly progressive polyneuritis by the thickening of the peripheral nerves and the familial incidence In neurofibromatosis it is rare to find uniform thickening of the superficial nerves polyneuritic symptoms are absent and the patient almost invariably shows some cafe au lait pigmentation of the skin Unless the thickened nerves can be felt it may be difficult or impossible to distinguish the condition from peroneal muscular atrophy unless a biopsy is made to demonstrate the characteristic thickenings of the sheath of Schwann Leprosy also causes a thickening of the peripheral nerves and where doubt exists a portion of the nerve should be excised and stained for lepra bacilli It should be noted that peripheral nerves may be visible and palpable although not thickened in certain wasting conditions e g diabetes hyperthyroidism Thickening of isolated exposed nerves e g the ulnar, may arise from repeated trauma

Prognosis

Harris and Newcomb and also Nattrass have described cases where the progress of the disease was marked by exacerbations and remission but the course usually is very slowly progressive over two or three decades Patients usually survive to middle life becoming increasingly incapacitated and finally bedridden

Treatment

The wasting of muscles should be treated by massage and passive movements Splinting and manipulation will prevent contractures and deformity When walking is difficult because of ataxia Frenkel s exercises may be employed with benefit Ionization of the hypertrophied nerves with potassium iodide has been tried

MYASTHENIA GRAVIS

Synonyms — Myasthenia gravis pseudo paralytica (Jolly) asthenic bulbar palsy (Strümpell) bulbar paralysis without anatomical changes (Wilks) Erb Goldflam s disease

Definition — A chronic disease of adolescent and adult life characterised by a variable paralysis usually symmetrical of the voluntary

muscles increased by exercise and disappearing shortly after rest The muscles affected most commonly are the external ocular muscles the bulbar and the cervical muscles There succeeds later a permanent paralysis which may be associated with a slight degree of atrophy The muscles implicated are readily fatigued by faradic stimulation The paralysis varies in severity from day to day and may disappear for months or years but the tendency of the disease is to a sudden unexpected fatal ending from respiratory failure

History

In 1877 Sir Samuel Wilks published in the Guy s Hospital Reports an account of a case of bulbar paralysis without anatomical changes The patient was a girl who had come to the hospital complaining of general weakness and that she could scarcely move about She had slight strabismus and difficulty in articulation For a month the case appeared to be one of lethargy from want of will rather than actual paralysis At the end of this period within three days she developed great dysarthria and dysphagia and was unable to cough though she could still get out of bed Shortly afterwards there was increasing difficulty in respiration and within a few hours the patient was dead A post mortem examination with histological examination of the bulb revealed no abnormality

This publication was followed next year by a paper from Erb describing three cases in which the chief symptoms were ptosis paresis of the muscles of mastication of the external ocular muscles and of the *muscles of the upper part of the face the tongue the neck and the ex*tremities Only one case proved fatal and no post mortem was made

To Jolly must be given the credit of establishing the disease as a clinical entity In his paper published in 1891 he pointed out the liability of the voluntary movements to tire throughout the body He took graphic records of the patients muscular contractions establishing one of the most striking features of the disease and he described the myasthenic reaction Jolly called the disease myasthenia gravis pseudoparalytica

Ætiology

The disease commences commonly between the ages of 20 and 35 although it may occur as late as 45 years The disease has been recorded in children of 9½ and 10 years It is commoner in females Of 91 cases

admitted to the National Hospital Queen Square London 40 were men and 51 women The disease is not familial or hereditary but it appears to have a relationship to diseases of the thyroid and thymus glands which have a tendency to run in families

The symptoms may become obvious after the acute specific fevers such as influenza typhoid scarlatina after intestinal disturbances chill prolonged fatigue and menstruation but there is no evidence that these are direct causal factors in producing the disease Syphilis and alcohol play no part in the causation Pregnancy often influences the course of the disease favourably in a remarkable way but confinement or the termination of lactation often is associated with exacerbations of the disease In female patients the symptoms often are worse during the menstrual periods

The association of myasthenic symptoms with exophthalmic goitre cannot be passed over Ophthalmoplegia associated with exophthalmos exophthalmoplegic ophthalmoplegia probably is a separate syndrome

Pathology

Central Nervous System — As a rule no abnormality can be found on gross or histological examination The nerve cells generally may show a diminution of basophil staining with Nissl s stain and show perinuclear chromatolysis such as has been described to occur normally in states of fatigue and exhaustion The cells of the oculomotor nuclei and the bulbar nuclei in some cases have shown vacuolation Recent capillary hæmorrhages when present are probably due to terminal respiratory failure

Muscles — Numerous histological studies of the muscles have failed to show any uniform pathological change apart from the rare occurrence of lymphorrhages (Buzzard)

Lymphorrhages — Lymphorrhages (Fig 21) are collections of mononuclear cells scattered throughout the muscles and viscera and they may be found in the central nervous system Lymphorrhages are difficult to find and are inconstant They are probably of most frequent occurrence in the muscles but they are met with also in the liver adrenals kidneys *lungs pancreas myocardium* and glands of internal secretions *Seen* in the muscles they are scattered in clumps amongst healthy muscle fibres usually in the vicinity of a capillary vessel Their relation to the lymphatics has never been demonstrated The bone marrow is normal

Thymus — A considerable proportion of cases show definite changes in the thymus gland simple hypertrophy or a thymic neoplasm Out of

56 cases with autopsies collected from the literature by Bell 27 cases i e nearly half presented some form of abnormality of the thymus gland and in 10 cases the abnormality found was a benign thymoma Obiditsch in a study of 9 cases of thymic neoplasm noted that only the benign thymic tumours were associated with myasthenia In cases of simple hypertrophy there is persistence of the thymus which may be enlarged or cystic Lymphosarcomatous changes have been observed in the thymus in this disease

Thyroid and Pituitary —The thyroid sometimes shows lymphor



Fig 71 Lymphorrhage in the biceps muscle from a case of myasthenia grav s

rhages interstitial fibrosis colloid degeneration of the fibrous stroma and proliferation of the epithelium with the formation of new vesicles The pituitary in Buzzard and Greenfield s case presented an adenoma

Patho enesis

It has been suggested that the muscular disability in myasthenia gravis may be due to some disturbance in the chemical mechanism con cerned in the transmission of nerve impulses to the muscles Sir Henry Dale and his coworkers have demonstrated the liberation of a substance resembling acetylcholin at the motor end plate following stimulation of

the motor nerves This substance normally is rapidly hydrolysed in alkaline medium by a cholin esterase a specific enzyme present in the blood It is assumed that in myasthenia gravis there is either an insufficient formation or an excessively rapid destruction of acetylcholin so that the nerve impulses fail to produce adequate muscular contraction Injection of eserine or its analogue prostigmin temporarily abolishes the symptoms by inhibiting the action of the cholin esterase and prolonging the action of acetylcholin

From electro myographic tracings Wolff Keutmann and Cobb concluded that the muscle exhaustion is due to some fundamental defect peripheral to the ventral horn cell Voluntary muscular contraction in this disease is accompanied by a paradoxical vasodilatation instead of vasoconstriction as in the normal The relationship of these muscular conditions to abnormalities of the thymus gland is not clearly understood Using dogs Adler asserted that by repeated grafting of thymus tissue from young animals he produced experimentally myasthenic weakness relieved by prostigmin like that of clinical myasthenia

The relationship between myasthenia gravis and hyperthyroidism has been investigated by Cohen and King These writers point out that while many cases of hyperthyroidism show a muscular asthenia relatively few cases of myasthenia gravis bear signs of associated hyperthyroidism The two diseases are believed to be quite separate Pathologically however they exhibit in common lymphorrhages in the muscles hyperplasia of lymphoid tissue generally and lymphocytosis in the blood In both diseases there may be lowered glucose tolerance and creatinuria on a diet free from creatin and creatinin

Symptoms

Allbutt has recorded a striking case which occurred in his practice before the disease was fully recognised in England It illustrates well how physical signs may be absent at the time of examination The patient was a girl of 18 years who began to talk as if with a potato in her mouth Allbutt says he put her to read from a book and she began well but soon her articulation was unintelligible She choked over her meals at the later meals of the day A provisional diagnosis of hysteria was made yet with reserve as the disorder of speech seemed a strange one Moral discipline was used by the mother and one day when the daughter came into her mother s bedroom to protest that she really could not help these eccentricities she fell to the ground suddenly turned blue and died at her mother s feet

The disease usually comes on gradually although in a few cases the onset has been sudden In more than half the cases ptosis or diplopia was the earliest symptom After the eye muscles the bulbar muscles especially those of mastication and deglutition are affected next most commonly then the cervical muscles and the muscles of the upper limbs and thorax The incidence of the disease is least on the lower limbs

Weakness appears in any of the voluntary muscles after exertion and it may be unilateral or more commonly bilateral and symmetrical Thus the waitress who carries heavy trays notices that towards the end of the day the tray will fall from her ever weakening arms The singer s voice will fail him towards the end of his song The commercial traveller who has many stairs to climb notices that towards evening his legs fail him they may give way and he falls to the ground After a night s rest the symptoms have disappeared only to reappear earlier the next day until at last the patient is unable to pursue his occupation

The disease may be confined to one group of muscles alone as the external ocular muscles or it may be widespread involving all the voluntary muscles in varying degree In the early stages where general fatigue after exertion with headache only is complained of it is of vital importance to distinguish myasthenia gravis from hysteria or neurasthenia the error that is made most frequently

Slight headache vertigo dull aching and other paræsthesiæ pains in the neck chest back and limbs may occur with the onset of symptoms

Ocular Symptoms —We test for myasthenia of the ocular muscles by looking for fatigue in repeated upward deviation of the patient s eyes Weakness of the orbicularis oculi is common causing ptosis often more marked in one eye than in the other (Fig 2_) Overaction of the frontalis rarely occurs in these cases owing to weakness of the occipito frontalis muscle and the patient compensates by tilting his head farther and farther back Lid retraction may occur also together w th a certain amount of dilatation of the pupils The upper lids may lag when the patient is told to look down and infrequent blinking may be present

Diplopia and often a frank strabismus occurs A striking feature of he diplopia is the alteration in the relative position of the two images at different times The paralysis always involves the eyes in terms of their conjugate movements and hence is of the nuclear type Inequality of the paresis on the two sides results in strabismus The external eye movements can be fatigued readily during examination and patients often complain of blurred vision after reading a few lines of print A jelly like nystagmus may be noted on extreme lateral deviation of the eyes These ocular palsies are characterised by their variability and their in

crease with fatigue Complete external ophthalmoplegia may occur (Fig 22)

Inequalities in the size of the pupils have been described but are very rarely met with The reactions to light may be sluggish or the reaction to light may be absent It seems likely that these changes are not accidental but are dependent on changes in the oculomotor nucleus At



Fig 22 Myasthenic facies showing ptosis greater in the left eye and compensatory wrinkling of the frontalis There is external ophthalmoplegia and the patient supports his drooping head by his hand

tempts to tire out accommodation or to fatigue the sphincter iridis by holding a bright light in front of the eye may succeed

Involvement of the muscles supplied by the trigeminal nerve causes one of the most constant symptoms of the disease difficulty in mastication This may be noticed towards the end of a meal or on eating tough foods when the lower jaw may drop The patient may assist the movements of his lower jaw with his hand during mastication or he support his lower jaw with his hand at rest (Fig 22) Slighter degrees of weakness

may be demonstrated by making the patient clench his teeth upon an envelope when it will be found that the paper can be readily withdrawn without tearing Clonic jerkings of the mandible resulting in biting of the tongue were noted in Buzzard s first case When the weakne s of the jaw muscles and lower facial muscles is great patients may complain of dribbling of saliva from the lips

Dysphagia from paralysis of the pharyngeal muscles is another com mon symptom and may be a cause of death from choking Weakness of the palate which may be of unequal distribution on the two sides causes regurgitation of fluids through the nose nasal voice and inability to blow out the cheeks *The palatal and pharyngeal reflexes may be diminished* or abolished

The tongue is affected less commonly than any of the other muscles innervated from the bulb The patient is dysarthric he can protrude his tongue but not for long and he may be unable to thrust it to the side into his cheek Involvement of the tongue frequently is accompanied by slight wasting and two lateral longitudinal furrows may sometimes be seen

Of 22 cases the laryngeal muscles were involved in 4 patients In no case was there total paralysis The voice may become hoarse or lower in pitch or the patient may be unable to shout or cry out or the voice may fail in counting from one to one hundred Myasthenic weakness of the abductors may show itself by the lessening in separation of the cords after a series of deep inspirations In other cases the abductors or both abductors and adductors are weak

Defects of speech may be due to weakness of the vocal cords the articulating apparatus lips tongue palate and jaw muscles or the respiratory muscles The patient may be unable to draw breaths deep enough for loud phonation Speech defects may be demonstrated by getting the patient to read aloud when the voice will soon tire

Facial Muscles — The facial appearance often is striking (Fig -3) There may be inability to wrinkle the brows or frown Ptosis often is marked and the facies generally mask like The weakness of the orbicu laris oculi often is profound as described above The lower facial muscles are affected frequently so that the patient cannot whistle or raise the upper lip to show his teeth Fluids may escape from the lips when the patient is drinking Total facial palsy is uncommon The weakness may be more marked on the one side than the other

Muscles of Trunk and Limbs — Of the muscles of the trunk and limbs those of the neck often fail at an early date The head tends to fall for ward or backward or when tilted forward or backward for long cannot be raised again The paraspinal and abdominal muscles may be af

fected shown by difficulty in rising from the recumbent posture without using the hands or inability to roll over in bed Sometimes a patient is unable to strain at stool from weakness of abdominal muscles

In the limbs the upper extremities are involved more frequently than the lower and the proximal muscles more than the distal We test for myasthenia in the arms by asking the patient to hold his upper limbs slightly abducted at the shoulders when they will be seen to fall slowly towards the trunk with an increasing fatigue paralysis or we may ask the patient to grip our hands repeatedly Weakness of the arms may be so



Fig 43 (a) Facies in myasthenia gravis The patient is trying to wrinkle his fore head (b) Myasthenic smile

great that the patient cannot feed himself When the patient tries to write the handwriting at first is free and rapid as he goes on it becomes slower and more illegible until he finally gives up the attempt

Involvement of the respiratory muscles is common The patient may complain of attacks of dyspnœa or cough The respiratory excursion of the chest wall may be noticed to vary from day to day Complete respiratory paralysis may be precipitated by any muscular effort by choking or by an emotional outburst and is the commonest mode of death Intermittence of the pulse towards evening has been described and attacks of tachycardia are not uncommon

Permanent palsies are most frequent in the muscles which are supplied by the bulbar nuclei and the cervical muscles The commonest permanent palsies are those of the orbicularis oculi of the external ocular muscles resulting in a partial or total external ophthalmoplegia and of the lower face and muscles of mastication The patient may be unable to keep his eyes closed when they are screwed up or a permanent ophthalmoplegia may result in constant diplopia

Persistent weakness in the extremities is encountered rarely

Muscular atrophy of slight degree occurs in a large proportion of cases It occurs usually in muscles in which there is some degree of permanent paralysis The tongue is a favourite site for atrophy and two lateral furrows may appear in the organ from this cause but atrophy may be seen also in the muscles of mastication and in the cervical and upper arm muscles Fibrillation does not occur except in the tongue where it is never well marked Buzzard has noted in one case the occurrence of spasmodic jerkings of the limbs when the patient was resting

Sensory symptoms such as aching in the limbs stiffness and even tenderness of muscle may be complained of by patients and may be attributed to muscular weariness There is never any objective sensory loss or disturbance of the special senses

The superficial *reflexes* are normal and the tendon reflexes usually are unaltered or rather brisker than normal although they may be absent The remarkable decrease of the knee jerks on repeated elicitation described by Strümpell Goldflam and Collins is an exaggeration of what occurs in many normal persons In Buzzard s case after exhaustion of the vastus internus by faradism the knee jerk could be elicited normally The plantar responses are flexor and the sphincters are never affected The *spinal fluid* is normal

The Myasthenic Reaction — Jolly in 1895 described the peculiar electrical reactions of the muscles in this disease Such reactions however are by no means constant and the typical myasthenic reaction is seen only in muscles showing conspicuous paralysis If a faradic current is applied to myasthenic muscles such as these there is at first a strong contraction which is however not maintained as in normal muscles After a certain number of faradic shocks the muscle reacts less and less until it shows at last no contraction to the strongest faradic currents Some volitional contraction however remains If we wait a few minutes and test again we find that faradic excitability has again appeared but it tires more rapidly than at first The responses of the muscles to galvanism are normal throughout the disease These electrical reactions are only of importance as being an easy way in some cases of demon

strating the abnormal muscular fatigue and the ability to recuperate It should be emphasised that the reaction is also met with in hyperthyroidism and is not peculiar to myasthenia gravis

The Prostigmin Test — A subcutaneous or intramuscular injection of 1 5 mgm of prostigmin with 0 5 mgm atropin sulphate to counteract any intestinal stimulation is made If the case is one of myasthenia gravis a return of power in the paralysed muscles should be observed five to twenty minutes after the injection This effect may last six to eight hours (Fig 24) While it has been observed that temporary improvement may also occur in cases of chronic bulbar palsy and polyneuritis under



Fig 24 (a) Myasthenia gravis showing double ptosis and compensatory backward tilting of the head (b) the same patient fifteen minutes after intramuscular injection of 1 5 mgm of prostigmin (Dr Blake Pritchard s case)

the influence of prostigmin the remissions of muscular weakness are never so dramatic as in myasthenia gravis

Sugar Tolerance — Disturbances of glucose metabolism are not uncommon Diminished glucose tolerance with an abnormally high and prolonged blood sugar curve may be found but increased sugar tolerance may occur also

Creatinuria — As in other muscle disorders creatin may be present in

the urine with a diminished urinary output of creatinin The amount of creatin excreted is never as great as it is in patients with muscular dystrophy

Persistence or Enlargement of the Thymus Gland — The chest should be examined always for neoplasm The difficulty of distinguishing clinically and radiologically between tuberculous lymph glands and enlargement of the thymus makes this examination of doubtful diagnostic value in children

Course and Prognosis

No feature of this disease is so marked as the irregularity of its course At one moment the patient may be bedridden with ocular palsies and dysphagia In a few days or weeks he may be well only later to develop symptoms again in the same or other parts of his body The occurrence of acute infections emotional excitement extreme muscular strain cold weather or the onset of the menses may precipitate a relapse but often it is quite impossible to account for a recurrence of the symptoms

Diagnosis

The response to an intramuscular injection of prostigmin prostigmin test see above is the most valuable diagnostic measure in doubtful cases The myasthenic electrical reaction and enlargement of the thymus though inconstant are important corroborative evidence and the finding of lymphorrhages in excised muscle will make the diagnosis where uncertainty exists

Where the onset of the disease occurs with transient aphonia and fatigue paralysis of the limbs the diagnosis must be made from hysteria Hysterical aphonia comes on suddenly the cough usually is not aphonic and the voice when regained is not hoarse The appearance of the vocal cords in tuberculous disease is characteristic

In cases with ophthalmoplegia the diagnosis must be made from disseminated sclerosis midbrain neoplasm and encephalitis lethargica The diplopia of disseminated sclerosis rarely is associated with gross ophthalmoplegia and is more constant and fixed from day to day than the variable diplopia of myasthenia gravis Pallor of the optic discs nystagmus absent abdominal reflexes or extensor plantar responses may be found in cases of disseminated sclerosis Certain midbrain tumors in the region of the superior colliculi if unaccompanied by headache vomit

ing and papilloedema may give rise to confusion but these cases tend to have increased cerebrospinal fluid pressure In encephalitis lethargica usually there is a history of sleep disturbance pupillary abnormalities are common and Parkinsonian symptoms may be present

When the disease begins with bulbar symptoms dysarthria and dysphagia the diagnosis from diphtheritic polyneuritis is made by the absence of history of sore throat and the specific diphtheritic paralysis of accommodation and the presence of the tendon reflexes In chronic bulbar palsy the small spastic fibrillating tongue with crenated edges is unlike the tongue of myasthenia gravis Pseudo bulbar palsy is characterised by the spasticity of the weak muscles and usually is associated with signs of pyramidal disease

When persistent palsies are present in the face the appearance may suggest a facial type of myopathy but the distinction is made by the involvement of the external ocular and bulbar muscles which never occurs in myopathies

It should be remembered that any bilateral paralysis of muscles supplied by the brain stem may be myasthenic When the onset of myasthenia occurs within a unilateral ophthalmoplegia or laryngoplegia the diagnosis may be in great doubt until further signs of the disease show themselves Myasthenic symptoms occurring for the first time in late life are more likely to be due to another organic disease simulating myasthenia gravis e g a malignant neoplasm with secondary deposits or a toxic polyneuritis

Treatment

The treatment consists of absolute rest in bed during the acute stage and the elimination of all fatiguing influences when the patient has recovered Massage and electrical treatment are harmful and should not be prescribed All solid food should be minced to lessen fatigue of chewing and the patient should never have to strain to empty his bowels

If the patient recovers sufficiently to be able to resume his occupation all unnecessary standing and speaking at his work should be avoided Such patients should never be allowed to run and walking must be restricted They should be warned that any emotional outburst is likely to prove harmful Warm underclothing should be worn as protection from cold and measures taken to ward off intercurrent respiratory affections Radiation of the thymus gland has been used when it presents a pathological appearance in radiograms Surgical removal of abnormal thymus tissue also may be considered

Prostigmin and Physostigmin — An injection of 1 5 to 2 5 mgm of prostigmin a substance analogous to physostigmin leads to temporary abolition or amelioration of the myasthenic symptoms The improvement in the affected mucles begins one hour after the injection and lasts as long as six hours To prevent the side-effects of the prostigmin colic nausea and collapse 0 5 mgm of atropin sulphate is given by injection with the prostigmin Two injections may be given daily Repeated injections however may lead in some cases to a grave increase in the symptoms after the beneficial effects of an injection have worn off It would seem advisable to restrict the use of prostigmin to periods when dysphagia or dyspnœa or profound general weakness threaten the life of the patient The drug can hardly be recognised as a routine treatment to keep the symptoms of the disease under permanent control Prostigmin seems to act by delaying the destruction of acetylcholin at the motor nerve endings by inhibiting the cholin esterase normally present in the blood

Prostigmin is costly and good results are also reported from the use of the less expensive physostigmin salicylate 7 5 to 10 mgm in water by mouth preceded by a mixture containing 1 to 1 3 c c of tincture of belladonna

Potassium Chloride — A large dose of potassium chloride (e g 10–20 gm) given by mouth in a copious amount of water sometimes causes temporary improvement lasting about two hours This substance may act by stimulating the ganglion-cells raising their excitability to preganglionic stimuli and to acetylcholin Side effects are diuresis nausea or diarrhœa A dose of 4 to 6 gm of potassium chloride taken shortly before the action of prostigmin has worn off may relieve the feelings of exhaustion and prolong the period of improvement

Ephedrin Sulphate — Regular administration of ephedrin sulphate 30 mgm thrice daily by mouth is harmless and seems to maintain some patients at an improved level of muscular power It is probably the safest and best drug for continued administration Harriet Edgeworth a sufferer from myasthenia gravis has reported how by taking 45 mgm of ephedrin daily for three years she became capable of moderate activity after a bedridden existence Glycin 3–6 gm twice daily has been given also with success but its value is doubtful

It should be remembered however in assessing the value of any form of therapy that complete or incomplete remissions are frequent in this disease and may last for weeks or years

The chief emergency to be treated is dyspnœa It is often caused as Strumpell points out by falling backwards of the tongue and may be re

lieved by pulling forwards of that organ The onset of respiratory failure should be treated by an intramuscular injection of 2 5 mgm prostigmin with 0 5 mgm of atropin sulphate and by artificial respiration The latter may be carried out manually or by intratracheal insufflation of air with an intratracheal anæsthesia apparatus or by putting the patient in a Drinker or similar respirator if such be available

Muscular Disorders in Thyroid Disease

Cases of hyperthyroidism frequently show considerable wasting of the skeletal muscles (Fig 25) an appreciable degree of muscular hypotonia as well as weakness and abnormal fatigue The muscles may give myasthenic electrical reactions The abnormal fatigability of the quadriceps muscles may be demonstrated by asking patients to step repeatedly from the floor onto a chair

Such patients sometimes describe crises of muscular weakness of gradual onset lasting perhaps half an hour when they are unable to move their limbs or they describe sudden transient giving way of the legs so that they fall to the ground

Three types of thyrotoxic myopathy are described by Russell Brain

(1) *Acute Bulbar Palsy Complicating Exophthalmic Goitre* —Very rarely a thyrotoxic patient may suddenly develop acute paralysis of the bulbar muscles with dysphagia dyspnœa and nasal regurgitation of fluids Death may occur in a week or two from asphyxia Such bulbar symptoms must be distinguished carefully from similar symptoms which occur as the result of pressure of an enlarged thyroid gland on the trachea and œsophagus

(2) *Thyrotoxic Periodic Paralysis* —Charcot described paroxysmal attacks of flaccid paraplegia with loss of tendon reflexes occurring in the course of exophthalmic goitre and he termed this Basedow s paraplegia Dunlop and Kepler have recorded four cases of periodic paralysis associated with exophthalmic goitre Their cases were all in males in no case was there any family history of recurrent paralysis and the onset was later in life than in family periodic paralysis Their patients had recurrent attacks of weakness in the legs or generalised muscular paralysis The attacks which lasted 24 to 36 hours frequently occurred in the night when the patient was in bed and the paralysis began in the proximal muscles and progressed distally On the day following the attack the patient complained of residual muscular weakness One such case examined during an attack showed loss of tendon reflexes in the paralysed limbs although the sphincters were unaffected and there was no sensory

disturbance During the attack the pulse rate rose to 180 per minute and the heart enlarged In one case the symptoms were cured by sub

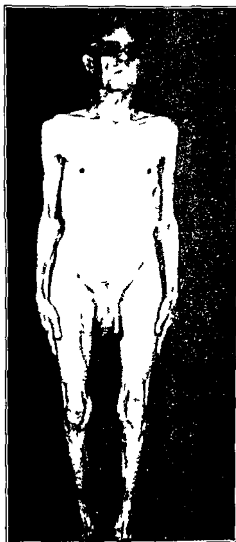


Fig 25 Muscular wasting in Graves Disease

total thyroidectomy but recurred three years later with recurrence of hyperthyroidism Morrison and Levy have described a similar case in a

man of 24 years with no family history of recurrent paralysis During the attacks the tendon reflexes could not be elicited Thyroidectomy did not cure the patient but changed the bouts of paralysis to crises of muscular weakness without actual paralysis In cases of periodic paralysis with hyperthyroidism Shinosaki produced attacks by thyroid feeding One of his cases came to autopsy and showed no abnormality in the muscles or spinal cord

(3) *Chronic Thyrotoxic Myopathy* — Russell Brain accepts that a condition resembling progressive muscular atrophy may complicate exophthalmic goitre In a disease like exophthalmic goitre where muscular wasting is so prominent it is difficult to accept amyotrophy as a symptom apart from general muscular wasting Sterling has described such a case with wasting of the hand muscles and gives references in his paper to other recorded cases

In all three conditions when there is hyperplasia of the thyroid tissue the symptoms are alleviated by subtotal thyroidectomy or by administration of iodine Such cases are distinct clinically from myasthenia gravis and family periodic paralysis

Permanent external ocular palsies in association with exophthalmos are described by Russell Brain as a syndrome which he calls *exophthalmic ophthalmoplegia* One or both eyes may be affected and the condition may be observed spontaneously in the middle aged and elderly males being affected more than females Other cases have been described after thyroidectomy for hyperthyroidism in patients with an abnormal basal metabolic rate The condition runs a benign course over some years The writer has never seen a case completely cured These ocular palsies unlike those of myasthenia gravis do not respond to prostigmin Histologically there is increase of retrobulbar fat and œdema of the extraocular muscles which show lymphocytic infiltrations and later fibrosis The pathological changes in the thyroid gland usually are not typical of Graves disease The fact that the syndrome may occur in myxœdematous patients indicates that the syndrome is not due to excess of thyroid secretion and the work of Smelser seems to indicate that it is rather an excess of thyrotropic hormone which may be responsible

Myxœdema with Myotonia — This has been described on a previous page of this chapter under the heading of Aberrant Forms of Myotonia

FIBRILLATION

Fibrillation (*syn* Myokymia) is the name given to rapid spontaneous flickering movements of individual muscle fasciculi sometimes seen in

the skeletal muscles It occurs in normal individuals and in a variety of pathological conditions The flickerings usually are intermittent and transient causing a quivering of the overlying skin and a subjective sensation of fluttering or light pressure moving from place to place

Fibrillary twitchings may occur spontaneously in relaxed muscle especially when it is exposed to cold air They may be elicited in response to tapping the muscle with the fingers or after active or passive stretching or shortening of the muscle when it is in the relaxed state The twitchings are seen commonly in the pectoralis major the deltoid the glutei and gastrocnemius When they affect the orbicularis oculi or orbicularis oris muscles they produce intermittent flickerings of the eyelid or lips of which the patient is disagreeably conscious

Muscles which show fibrillation often also exhibit myotatic irritability When the muscle is sharply tapped with a reflex hammer or lightly pinched in the fingers a local visible transverse ridge of contraction appears which persists for a second or two

Both fibrillation and myotatic irritability probably are due to a local disturbance of muscle metabolism It seems probable that they are not due to active innervation of the muscle fibrils

Fibrillation may be met with in the following conditions (1) In normal individuals particularly in the orbicularis oculi muscles It is sometimes popularly called live skin (2) In exhaustive and toxæmic states e g phthisis lead poisoning and in neurosis (3) In sciatic neuritis fibrillation may be seen in the gastrocnemii gluetei or hamstrings In incomplete facial palsy particularly when it arises from compressive lesions of the facial nerve in the Fallopian canal and in facial hemispasm continuous vermiform movements may be observed in the facial muscles on the affected side (4) In combination with muscular wasting and alteration in the tendon reflexes fibrillation is highly characteristic of the active phase of motor neurone disease

In the bulbar form of this disease a highly characteristic clinical picture is that of a small wasted tongue lying in the floor of the mouth its muscle bundles animated by continuous flutterings which impart no movement to the organ The wasting and fibrillation may be confined to one half of the tongue In motor neurone disease the fibrillation may appear in muscles which not yet have been affected by the atrophy which it heralds

Fibrillation does not occur in acute destruction of the ventral horn cells due to acute poliomyelitis or polyneuritis It is observed occasionally in peroneal muscular atrophy

The treatment of fibrillation is by general care rest and massage

man of 24 years with no family history of recurrent paralysis. During the attacks the tendon reflexes could not be elicited. Thyroidectomy did not cure the patient but changed the bouts of paralysis to crises of muscular weakness without actual paralysis. In cases of periodic paralysis with hyperthyroidism Shinosaki produced attacks by thyroid feeding. One of his cases came to autopsy and showed no abnormality in the muscles or spinal cord.

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wrinkled skin of the abdomen The affected infant cannot cough and dies in a few months of bronchopneumonia This condition is associated with defects in the urogenital system Defects of the diaphragm with eventration of the viscera into the thorax are also met with

Myoclonus

Definition —The term myoclonus is used to describe sudden shock like clonic contractions of muscles or parts of muscles

The characteristics of a myoclonic twitch are as follows The rate of the contractions varies from ten to one hundred per minute and they follow one another at irregular intervals without rhythm A sudden contraction in one muscle is followed by an equally sudden contraction in another or the spasm may be repeated in the same muscle several times The distribution may be in asymmetrical muscles over the trunk and limbs The myospasms affect the upper limbs more commonly than the lower limbs and the proximal rather than the distal muscles The face is seldom if ever involved The movement commonly is confined to an isolated muscle or to part of a muscle rarely several muscles are affected A coordinated twitch of a group of synergic muscles never occurs and there is not any conspicuous relaxation of the antagonistic muscle The distribution of the contractions is never determined by the peripheral nerve or the root supply

The myospasms cannot be reproduced by any volitional effort for example the contraction may affect one rectus abdominis a muscle which cannot be voluntarily contracted apart from the rectus abdominis of the opposite side It is said that unstriped muscle e g bladder may be involved as well as striped muscle

The strength and effect of the contractions vary in degree usually they have little or no effect in moving the limb although rarely a severe twitch will disturb the patient s equilibrium and throw him to the ground Simultaneous laryngeal and diaphragmatic spasms may cause the patient to emit a curious grunt the speech may be cut short by a spasm of the tongue or throat muscles or spasm of the expiratory muscles may cause a word to be blurted out suddenly Voluntary movements may diminish or accentuate the myospasms A spasm may be evoked in the rectus abdominis by exposing the patient s abdomen to the cool atmosphere or it may be produced by irritation of the skin or by percussion of the muscles The electrical excitability of the affected muscles is unaltered but spasm may be initiated by application of electrical currents

Arthritic Muscular Atrophy

Muscular wasting is a common accompaniment of monoarticular or polyarticular arthritis especially rheumatoid arthritis It affects mostly the extensor muscles in the neighbourhood of the affected joint or joints and the whole muscle belly shows equal atrophy Clinically the condition is associated with pain in the joint and with increased myotatic irritability and increase in the tendon reflex of the affected muscles Contractures sometimes occur Microscopically the muscle fibres show simple atrophy without fat replacement The microscopic changes of myositis are not observed

The condition possibly is to be attributed to nutritional disturbance following on altered blood supply the pain in the joints causing an alteration in vasomotor tone in the segmentally innervated muscles Disuse may also play a part in the production of the atrophy

Congenital Aplasia of Muscles

Definition — This is a congenital defect of development of one or more muscles or part of a muscle often causing pronounced disability Such a defect is unassociated with progressive disease of the muscular system or neuraxis In rare cases the disease is familial

Pathology — Microscopically the affected muscles may show variability in the size of the fibres proliferation of the sarcolemma nuclei and increase in interstitial tissue The corresponding ventral horn cells in the spinal cord are diminished or absent but this probably is secondary to the muscle condition

Symptoms — The defects usually are unilateral and confined to one muscle or group of muscles Not only the sternal part of the pectoralis major is absent but the aplasia may affect the pectoralis minor the trapezius quadriceps serratus magnus semimembranosus deltoid latissimus dorsi sternomastoid rhomboid spinatus or biceps

Defect in the pectoral muscles may be associated with imperfect development of the nipple malformation of the hand syndactyly defects in the thoracic wall or scapula and the presence of cervical rib

Rarely aplasia of bilaterally symmetrical muscles may be met with Thus the trapezius sternomastoids lower half of the pectoralis major may be absent on the two sides Congenital defects in the ocular muscles and congenital weakness of the facial muscles are also met with

Congenital absence or defects in some or all of the abdominal muscles are recorded The abdominal viscera are held in only by the thin

malaria probably should be classed with the group of cases associated with encephalitis

Hyperpnœic Myoclonus — Artificial deep breathing for a period of about thirty minutes will in a normal individual induce tetany In a small proportion of normal persons an epileptic fit may be so induced It has been observed that in some cases of spinal cord compression artificial deep breathing produces a temporary myoclonus in the muscles below the level of the lesion Only the trunk muscles and the large proximal muscles of the limbs are involved the distal muscles escape In intramedullary lesions this curious phenomenon is said to be absent

Myoclonus in Degenerative Encephalopathies — Myoclonus has been noted in cerebral diplegia torsion dystonia in infantilism (Purves Stewart) and associated with nystagmus Ramsay Hunt in addition to the cases which he calls dyssynergia cerebellaris myoclonica has described two cases of Friedreich s ataxia who developed myoclonus and epileptiform seizures At autopsy on one of the cases there were cord changes of Friedreich s ataxia with atrophy of the cells of the dentate nucleus and the superior cerebellar peduncles

Rhythmical Myoclonus

Involuntary rhythmic movements sometimes are observed in the palate tongue pharynx larynx diaphragm and in the intercostal and abdominal muscles The movements are quick (50 to 240 per minute) rhythmic and abate only when the muscles involved are used involuntarily or reflexly Guillain and Mollaret describe two cases One was a man of 55 years complaining of vertigo and diplopia who presented synchronous rhythmical movements of the soft palate pharynx larynx and diaphragm at a rate of 120 per minute The lesion in this case probably was syphilitic and the blood Wassermann reaction was positive Their other case was a hemiplegic woman of 60 years with right sided pyramidal and cerebellar signs The myoclonic movements of the palate pharynx and larynx were in this instance unilateral confined to the right side The right half of the diaphragm was also affected

A variety of pathological conditions can cause this syndrome According to Guillain and Mollaret it is associated with lesions of the central tegmental and dentato olivary tracts which produce a peculiar pseudo hypertrophy of the inferior olivary nuclei The clonic movements tend to occur on the side opposite to the diseased inferior olivary nucleus

The phenomenon has been termed *palatal nystagmus* , but the name nystagmus is best reserved for purely ocular phenomena The name

Pathology of Myoclonus

Much speculation exists as to the site of the lesions responsible for myoclonus Clinically there is a close association with epilepsy and with inflammations and degenerations involving the cortex

Symptomatic Myoclonus

Myoclonus in Epilepsy — Myoclonic movements are not infrequent in chronic epileptics Russell Reynolds has stated that seventy five per cent of all epileptics have some kind of inter paroxysmal motor disorder of the type of myoclonus These movements usually are referred to by patients as the jerks and they have been known to precede the onset of fits for months or even years They affect the upper limbs and trunk muscles chiefly are almost always bilateral and they may be attended by transient loss of consciousness Such cases probably form the connecting link between true epilepsy and myoclonus epilepsy

Ramsay Hunt described as an independent disease a rare malady which he terms *dyssynergia cerebellaris myoclonica* Epileptiform fits and myoclonus begin between the age of seven to seventeen years and several years later there appears a cerebellar ataxia confined at first to one side of the body It is extremely doubtful if this is an independent entity Fits are recognised to occur in degenerative cerebellar diseases and, as we have noted above myoclonus is not infrequent in those subject to epilepsy

Myoclonus in Encephalitis — Myoclonus may appear as a symptom of encephalitis lethargica or in other forms of encephalitis in the acute or chronic stage of the disease Buzzard and Greenfield in 1919 and later Krebs described myoclonus as a residuum or late sequela of encephalitis lethargica The myoclonus may be the only symptom or more commonly it occurs with other evidence of chronic encephalitis e g paralysis of accommodation diplopia Parkinsonism oculogyric crises etc Such myoclonic movements often are slight and may appear only when the patient is fatigued

Usually they cause no disablement and in themselves should not be regarded as a serious prognostic symptom Goodkind has described a case in which the myoclonic movements were manifest only on exposure of the eyes to bright light The patient was a young woman with a history of previous epileptiform convulsions following encephalitis at the age of 13 years The myoclonus which is rarly observed after an attack of herpes zoster after Sydenham s chorea (Bergeron Henoch) and in cerebral

quency Intermissions of several days when the patient is bright and free from attacks are not uncommon

Psychical changes are evident from the earliest years of the disease Apathy irritability periods of somnolence psychical equivalents or catatonia are described leading to progressive intellectual impairment and terminal dementia or a manic depressive psychosis

In the first stages of the disease commonly after the first decade the epileptic attacks cease while the myospasms increase The patient falls into a state of somnolence and becomes rigid and bent he salivates and sweats profusely Death occurs from inanition in status myoclonicus or status epilepticus or from some intercurrent disease such as tuberculosis pneumonia or nephritis

The myoclonus which characterises the disease is persistent and severe and affects particularly the proximal muscles The shoulder girdle muscles the pelvic girdle muscles the throat face and lastly the diaphragm pharynx and larynx may be affected

In van Bogaert s cases involuntary movements resembling those of choreo athetosis or torsion dystonia were observed in addition to the other symptoms

Diagnosis — The diagnosis from hereditary ataxia with epilepsy may be impossible during life but myoclonus-epilepsy should be suspected in cases with recurrent convulsions severe and persistent myoclonus and progressive dementia A family history of the disease may be obtained

Myoclonus epilepsy has to be distinguished from Huntington s chorea This latter disease begins later in life usually between thirty and forty years and there is no periodicity in the symptoms rarely is it combined with epilepsy The movements of Huntington s chorea comprise synergic contractions of groups of muscles In myoclonus-epilepsy the patient soon loses the ability to walk while in Huntington s chorea the power of walking is not lost until the final stage of the disease

The differential diagnosis has also to be made from the twitchings of muscles which occur in the interval between Jacksonian fits and constitute the syndrome known as the *epilepsia partialis continua* of Kojewnikoff

The prognosis is quite hopeless although the patient may survive to the age of fifty or sixty

Acute Algo Myoclonic Encephalitis

In 1920 Sicard and Kudelski described four cases of a disease they called acute myoclonic encephalitis They recognised it as a form of

velo palatine clonus is better, as the rhythmic sequence of the discharge seems to be physiologically most allied to the reflex pattern of a sustained clonus the sequence started by one stimulus exciting the next The phenomenon differs from myoclonus in that it is rhythmic and confined to one or more groups of muscles

THE MYOCLONIAS

There are however two main types of myoclonic disease which may be considered as entities (1) myoclonus epilepsy and (2) acute algo myoclonic encephalitis

Myoclonus Epilepsy

Definition — This is a heredo familial disease characterised by epileptiform convulsions myoclonus and progressive dementia

History — It was first described by Unverricht in 1891 in a monograph entitled Uber Myoclonie He described a family of five brothers and sisters all of whom suffered from epileptiform convulsions in addition to myoclonus with progressive dementia

Lundborg in 1903 in a monograph on Die Progressive Myoclonus Epilepsie pointed out that the disease was inherited as a recessive In 1929 van Bogaert published an account of a family in which three generations were affected His cases exhibited movements resembling choreo athetosis and autopsy findings were recorded in two of the cases

Pathology — In the cytoplasm of the ganglion cells are found numerous globoid bodies resembling amyloid in that they stain with anilin dyes and silver salts (Freeman) The characteristic ganglion cells are found particularly in the dentate nuclei substantia nigra red nuclei and optic thalamus The neurons themselves show little degeneration A fine zone of gliosis may be present in the superficial layers of the cerebral cortex

In the cases described by van Bogaert the characteristic ganglion cells are absent He found widespread degenerative changes in the prefrontal and motor cortex the corpus striatum and the olivary nuclei

Symptoms — The onset usually is in early childhood with petit mal attacks or nocturnal convulsions In a year or two myoclonic movements appear and gradually become more frequent and severe The child may be thrown to the ground by the myoclonic jerks and may have to be padded or splinted to prevent injury in bed As the myoclonic movements become more severe the convulsions lessen in fre

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Acute Algo Myoclonic Encephalitis

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epidemic encephalitis of which disease they regarded it as a distinct type probably a meningo radicular variety and they called attention to the resemblance of their cases to the condition which Dubini in 1846 called *electric chorea*

Involuntary movements of great variety are common in all types and stages of epidemic encephalitis and the term myoclonic encephalitis has been used loosely by many subsequent writers It should be employed in Sicard s sense alone and as a purely descriptive term without pathological basis (Walshe)

The disease has an acute febrile onset with shooting pains of great intensity in the limbs and trunk These severe pains are followed by widespread myoclonic movements which appear first in regions where the pains are felt first The abdominal muscles are affected most frequently The pupils are widely dilated there is tachycardia and profuse sweating Speech becomes indistinct owing to myoclonic movements Insomnia is the rule and later there is delirium In three such cases described by Ellis leucocytosis was present in the blood with a slight relative increase in the polynuclears The cerebrospinal fluid may show pleocytosis increase of albumin and globulin and alteration in the Lange gold curve Ellis s Sicard s and Kudelski s cases all ended fatally In two of the cases described by Sicard clonic contractions of the upper limbs gave place after several days to a paresis of a peripheral type wrist drop in which the supinator longus escaped Fibrillary twitching as well as myoclonus was noted in the affected muscles

The patient may pass into a lethargic state with ocular palsies as in the ordinary type of encephalitis lethargica or death may occur in coma after an illness of two to three weeks The mortality rate is high

Treatment of the Myoclonias

Bromides and luminal 30 mgm (gr $\frac{1}{2}$) t i d are the most useful sedatives to employ in the treatment of the myoclonias In myoclonus epilepsy many of the cases are freer from symptoms in the seclusion of an institution In myoclonic encephalitis daily intravenous injections of 1 to 5 c c of a sodium salicylate solution (1 gm in 5 c c of water) have been tried

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CHAPTER XXXIII A

PSYCHOANALYSIS

By CARL BINGER

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HISTORY

Since the beginning of this century psychiatry like clinical medicine, has concerned itself more with the causes of disease than with its description and classification In other words it has become more dynamic in its approach As medicine had its great masters of description like Sydenham so psychiatry had its Kraepelin

The birth of modern psychotherapy can be traced to France with the work of Liebault of Bernheim and of Charcot The effect of their observations is by no means yet spent It has profoundly influenced all of modern psychiatry It was to Charcot s clinic at the Salpetriere that Freud came as a student physician in 1885 Here it was that he witnessed the experiments with hypnotism on hysterical patients Although Freud always acknowledged Charcot as his venerated teacher he pays tribute as well to Liebault and to Bernheim of the Nancy School for their extremely impressive demonstrations of suggestion[1]

Almost one hundred years earlier an Austrian physician who had studied in Vienna having made experiments on the supposed curative power of the magnet brought his theory of animal magnetism with him to Paris where he devoted himself to curing disease This was Franz

Psychoanalytical Theory

Psychoanalytical theory was derived empirically and inductively from observation. It has therefore the structure of a science and can be taught. It is not a philosophy of life and Freud resisted all efforts to elevate or derogate it into a "system." He once said: "I learned to restrain speculative tendencies and, following the unforgotten advice of my master Charcot, I looked at the same things again and again until they themselves began to talk to me." For this reason, although undoubtedly for personal ones too, Freud fought those among his pupils like Adler and Jung who seceded from him and who struck out on their own to devise schools of wisdom and philosophical systems.

What Freud did was to discover a new method of investigating the psychic life. The method known as *free association* was the natural outgrowth of the cathartic procedure which Freud gradually abandoned because he found the original traumatic theory an inadequate explanation of psychoneurosis and therapy by hypnotic abreaction of little permanent value. The "cure" under hypnosis was, moreover, purely a symptomatic one and depended on maintaining a personal relationship between patient and physician. What Freud discovered is now pretty generally known, namely, that patients will reveal, even when awake, many important things concerning themselves if the physician listens attentively and sympathetically. But Freud listened as attentively to the apparent irrelevancies as he did to more reasoned utterances, especially when they were accompanied by evidences of emotion. In applying this passive attention to his patient's outpourings, Freud soon observed that thoughts are not always connected in the logical and orderly sequence of usual conversation. If the patient is sufficiently relaxed and confident, his thoughts will tumble out in a manner that at first does not seem to make sense. It is to Freud's credit that he discovered the rhyme and reason behind these apparently unrelated thoughts. He concluded that logical conscious thinking depended upon the constant exclusion of intruding thoughts. These are kept out of focus or "repressed" because they seem illogical, trivial, embarrassing, repugnant, or because they may undermine self esteem. Freud therefore demanded of his patients that they try to lay aside for the moment all self criticism and that they make the effort to be as truthful as possible by relating *everything* that came into their minds. He discovered that their flow of ideas had indeed a kind of inner logic, that ideas which seemed to pop up at

Anton Mesmer for whom the occult art of mesmerism was named His seances were investigated by a commission of physicians and scientists appointed by the French government They denounced him as an im poster Only one of them dissented This was the botanist de Jussieu who wrote a minority report He was convinced that an investigation into the forces behind animal magnetism would be highly illuminating and he realized that imagination was an important factor in Mesmer s seances

One of the commission was Benjamin Franklin, who agreed with the majority in their conclusion that some sick persons of the common people are the only ones who feel any effects of animal magnetism Lacking his usual shrewd perspicacity, he fell in with his colleagues' exclusive demand for physical proofs, and he missed thereby the oppor tunity of becoming the discoverer of modern psychology But Frank lin then was old in poor health and completely absorbed by his diplo matic duties Mesmer himself did not understand what lay behind animal magnetism, not even when d Elson his French protagonist in a response to the Academy s report, declared ' The new agent might indeed be no other than imagination itself whose power is as extensive as it is little known If treatment by the use of the imagination is the best treatment why do we not make use of it " It has been said that with these words Dr Charles d Elson laid the corner-stone of modern psychotherapy [3]

The learning that in its crude form had been brought from Vienna to Paris by Mesmer was returned somewhat refined nearly a century later by Freud, who took it from Paris back to Vienna There he urged the internist Josef Breuer to resume the "cathartic procedure', which had remained dormant for a number of years, and there too Freud having been disappointed with the successes of electrotherapy, turned to treatment by suggestion in deep hypnosis As is well known, Freud for a while joined forces with Breuer The fundamental fact of Breuer s dis covery was, to use Freud s own words, 'that the symptoms of hysterical patients depend upon impressive but forgotten scenes of their lives (traumata)" The therapy founded thereon was to cause the patients to recall and reproduce these experiences under hypnosis (catharsis) and the fragmentary theory deduced from it was that these symptoms corresponded to an abnormal use of undischarged sums of excitement (conversion)[4] This theoretical conception was the joint product of Breuer s and Freud s minds It represents the corner stone on which the subsequent structure of psychoanalysis was erected

this language requires like the language of any science a long period of study The best and the essential preparation is for the student himself to have been analyzed This will give him a familiarity and an at homeness' with his own unconscious processes and will enable him by just so much to understand his patients

The most direct approach to the unconscious will be found in dreams where this primitive type of thinking already alluded to is so outspoken Freud soon learned to distinguish between the manifest content of a dream usually expressed in the idiom of the dreamer s daily life and its latent or hidden content which can be deciphered only through obtaining the ideas associated with the imagery of the dream

For example A patient dreamed of a small alligator who vomited blood all over the keyboard of a piano This the manifest content meant nothing to the patient but she recalled that at the age of twelve she had had a pet alligator, which she used to dress up in doll s clothes and wheel about in a doll carriage She could do nothing more with the thought of vomiting blood until the analyst piecing together the age of twelve and the probable onset of menses suggested that the vomiting of blood on the piano keys (a good example of displacement of one organ by another) perhaps referred to some menstrual accident The patient then recalled the sudden hemorrhage which a governess had experienced while in her company and only the next day did she remember that once when she was at the circus with her mother and her three younger brothers her mother had left a pool of blood in the chair of the box which they occupied The little girl did not know just what this meant but she was frightened by it and took great pains to conceal the occurrence from her brothers This patient s mother is an accomplished pianist who was introduced into the dream by the image of the keyboard

This abridged version of a dream only partially analyzed and its manifest and latent content gives some notion of the extraordinarily condensed and distorted character of the language of the unconscious Sometimes it can be understood only by inference and reconstruction just as an archeologist reconstructs a pot from a small shard or a skull from a mandible or as a geologist reads the past from present erosions or from the impression that fossils have left in rocks There will always be something of the happy guess in dream interpretation but the wise and experienced analyst never foists his interpretation on a patient He throws out a well timed suggestion based on the evidence at hand with hope that further associations will be evolved and that a piece of forgotten

random were connected by the feelings, attitudes and emotions of the thinker

This discovery led to the necessity of constructing the theory of an unconscious mental life often quite remote and unrelated to the conscious life of every day He conceived of the unconscious as a "special region of the mind [6] not of course anatomically located where thoughts feelings impulses wishes and instinctual drives existed, blind and inarticulate Here they exerted a kind of pressure for expression in order to relieve the tension which they set up This pressure for expression revealed itself in the seemingly chance verbal productions of his patients and also in their behavior, gestures, memory defects slips of the tongue their occupations and preoccupations and often in the symptoms of which they complained It was with this method of free association that Freud set out to explore the unconscious mind

If one may be permitted to use the expression unconscious thinking' it can be said that thinking at this level is of a much more primitive infantile order than is usual conscious thinking For example, the laws of nature do not prevail time and space relationships have no validity gravity does not exert its accepted pull (how often in dreams do people fly over house-tops) one and the same person can be both loved and hated or can be substituted for another because of some slight physical resemblance or because of a similarity in feeling toward them, one part of the body is often displaced by another, long abandoned beliefs in magic and fairy stories are freely resorted to, and many feelings and emotions never achieve ideational content at all but express themselves by bodily sensations or by the discharge of the vegetative nervous system So, hate may express itself in the form of diarrhea stubbornness by constipation disgust by vomiting and fear by a great variety of bodily disturbances without any of the underlying emotions or affects as they are called in psychiatry ever making themselves more directly apparent

The Task of the Psychoanalyst

The task of the psychoanalyst then is to learn the language of the unconscious so that the hidden forces (libido) in his patient become known to him and can be liberated for productive living rather than for the formation of symptoms Freud speaks of pursuing the libido 'in the analytic treatment aiming always at unearthing it making it accessible to consciousness and at last serviceable to reality [7] To learn

and brothers and sisters and nurses play their vital role too and remain forever the characters which people the drama of his maturity With its genius at legerdemain the unconscious can play tricks and substitute teachers and employers for fathers colleagues and rivals for siblings wives and sweethearts for sisters and mothers Even the sex of the individual does not hinder his being displaced or substituted by another The unconscious thinks nothing of introducing a man for a woman or vice versa if there is some slight similarity between them or if the feeling toward them is analagous

THE PATIENT AND THE ANALYST

Bearing this in mind the analyst will not be surprised to find that he himself soon takes on in the patient s thoughts attributes and characteristics which he may not in reality possess The patient makes of him what he needs him to be This is all the truer because proper analytical technique depends on the physician s keeping his own personality his predilections and moral judgments out of the relationship The patient then projects his feelings and needs onto the analyst and tries to make him conform to his own fantasy This phenomenon so surprising to the tyro and to the patient alike is known as transference so called because the patient transfers to the analyst feelings and attitudes actually belonging elsewhere usually to important persons connected with his childhood In this unusual relationship the patient loses in greater or lesser degree the common sense realistic attitude of an intelligent human being seeking cure of an illness and instead shifts to a neurotic one in which childish and emotional features may predominate From these neurotic attitudes the analyst tries to extricate his patient Such attitudes need not immediately make their appearance The patient may begin with eagerness to conquer his difficulties he may be acutely aware of his neurotic handicaps and be ready to go to great lengths by sacrificing both time and money to overcome them and yet gradually and subtly this attitude gives way to another one He appears now to be indifferent to the outcome of the treatment He may become touchy irritable flirtatious demanding and spend his time battling with the analyst and trying to trick him into doing what he does not intend to do[10] His reason for coming for analysis is no longer to get well but rather to extract some kind of emotional satisfaction from the treatment He wants to be waited on taken care of advised as to major or even minor decisions helped in practical matters and generally reassured praised and comforted and loved

biographical material will come to light When this occurs, the patient usually feels that something has clicked , or on the other hand, if sensitive material is being approached he may have need to reject the interpretation completely The art of analysis depends greatly on the proper timing of interpretations In any case, the purpose of interpretation is not primarily to unearth a traumatic experience, as Breuer set out to do in his cathartic method It is rather to remove resistances so that the patient will continue to associate freely and thus gradually revive the prevailing affective attitudes of his infancy and childhood Although resistance is the chief stumbling block to analysis from another point of view it is the essential material with which we work It is the mountain through which we dig our tunnel or the rock through which we drill our well

Repression

Anyone who uses the free association method will quickly become aware of the fact of resistance In spite of the most conscientious efforts on the part of the patient to tell everything he cannot be completely successful in this enterprise Certain thoughts are almost automatically repressed or sucked back into unconsciousnes Patients find themselves unable to tell or they will babble along about the trivialities of their daily lives There are innumerable ways in which resistance betrays itself to the analyst They may run the gamut from forgetting appointments or being late to concerted efforts on the part of the patient to ingratiate himself into theoretical and philosophical discussions Anything to draw a red herring across the trail All the while the patient although ostensibly and honestly trying to cooperate is fighting to keep from his mind the very things he is also striving to reveal These are not usually the peccadillos and indiscretions or even the vices of adult life They are much more likely to be what was originally on the surface in childhood but kept secret to avoid adult reproof thoughts and feelings, fantasies and emotions often intimately bound up with such simple bodily activities as sucking, biting defecating and urinating It is through these functions that the infant establishes his first contacts with the world of objects around him functions which are used not only to satisfy bodily needs but to express emotions And foremost in emotional importance in this world because his survival depends upon her looms the figure of his mother who may become to the patient in later life the unconscious prototype of all other women Father

and brothers and sisters and nurses play their vital role too and remain forever the characters which people the drama of his maturity With its genius at legerdemain the unconscious can play tricks and substitute teachers and employers for fathers, colleagues and rivals for siblings wives and sweethearts for sisters and mothers Even the sex of the individual does not hinder his being displaced or substituted by another The unconscious thinks nothing of introducing a man for a woman or vice versa if there is some slight similarity between them or if the feeling toward them is analagous

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Transference Neuroses

In one form or another this period, known as the "transference neurosis" occurs in every analysis of normal as well as neurotic people It is a time when the emotions which they are experiencing are more important to them than is recovery During this period they appear to be dominated by the major, unresolved, unconscious problems of their childhood" These are reproduced and lived out in the transference situation, the patients striving always to get what they failed to get in childhood or never learned to do without Recovery depends upon working through this complicated relationship that contains within it the original infantile conflict

In a sense the "transference neurosis" is an artifact, experimentally produced in the analytical situation, or rather, it is a condensed, telescoped version of the patient's life history in which his prevailing conflicts discontents and the imperious unrealistic demands of his childhood are revived and exposed This gives the analyst the opportunity to deal with them in pure culture, so to speak and in a more or less controlled situation, because many of the difficulties which neurotic individuals experience in life have to do with their relations to others, and these are now centered largely on the person of the analyst

It is a period therefore in which the patient often becomes sicker His symptoms may increase, and he may develop new ones This is painful for him, but he relinquishes his fantasies with great reluctance He even enlists his most intense love feelings toward the analyst, not to cooperate with him but as further resistance, demanding, sometimes even expecting immediate gratification rather than ultimate cure The proper and skillful handling of this situation requires tact, subtlety and a clear-sighted steadiness of purpose on the part of the analyst He strives always to see behind the intensity of his patient's feelings recognizing in his inordinate need to be loved evidences of anxiety or other overwhelming emotion such as hate or guilt His calm and steadying presence finally makes it possible for the patient to come to grips even with these devastating feelings

The term "transference neurosis", as here used to designate a certain phase of analytical treatment was used also by Freud in a kind of diagnostic sense Those people capable of reacting in the manner described were said to be suffering from a "transference neurosis", a category including the chief psychoneurotic illnesses especially those of the hysterical phobic and obsessive compulsive types These Freud dis

tinguished from the narcissistic neurosis schizophrenia for example which Freud believed did not lend themselves to this kind of therapy because they were incapable of developing a transference neurosis He may have been correct in this formulation, but we do know, on the other hand that many other individuals besides those suffering from hysteria or obsessive compulsive neuroses are capable of developing and experiencing intense transference relationships This holds true for some schizophrenics for example who are not too lost in their autistic fantasies It is also true of certain manic depressives when they are neither too elated nor too depressed And it is also known that so called neurotic characters psychopathic personalities epileptics and a variety of other mentally or emotionally disturbed people react with intense transference feelings from which however it may be far more difficult to extricate them than it is in the psychoneurotic group for which the method of psychoanalysis was originally designed

There is reason to believe that transference is a far more widely distributed phenomenon than is to be gleaned from technical treatises alone Even normal love partakes of it Much of the exaggerated ecstasy of falling in love contains within it some of this tendency to project on to the loved one attributes which we need him to possess The blindness of love consists not in loss of vision but in a kind of selective vision We see what we want and need to see And the raiment in which we clothe the one we love is made up of the visions of our childhood The good wife then becomes mother sister nurse companion courtesan all rolled into one and the good husband father brother friend even mother But even in much less intense emotions than those of love this same process can be seen at work In the relationship of teacher and pupil of lawyer and client of priest and parishioner of officer and men of political leader and constituents of orator and audience of dog and master in all of them the authority and magic and power of the one is derived in part from the projected needs of the other If this is true in these situations how significantly true is it of the physician and the surgeon whose power to heal depends in such large measure on the personal relationships which he establishes with his patients Much of the success of his therapy specific as well as non specific will depend on these imponderables

If then the tendency to form transference is ubiquitous in man it alone cannot be used as a criterion for the application of psychoanalytic therapy The method has been applied extensively both here and abroad to almost the whole category of mental and emotional illness

Analysts vary greatly in their willingness to apply it to others than the classical psychoneurotic group for which it was intended The rash and the courageous the resourceful and imaginative will often take on cases that the conservative and cautious will shun This is probably also true of surgeons although in their work prognosis is more soundly established on statistical data than in the case of psychoanalysts

The Procedure

Before beginning psychoanalytical treatment it is, of course necessary to have arrived at a diagnosis and to have some notion as to what outcome may be expected These facts are learned from an ordinary psychiatric interview Some analysts have found that a too exhaustive preliminary investigation interferes with the patient's willingness or ability to talk freely Many modern analysts enlist the help of clinical psychologists whose methods of testing sometimes afford remarkable insight into the nature of the difficulty When the decision has been made to use the psychoanalytical method the patient is briefed in detail as to what is expected of him The number of visits per week are agreed upon They may be as many as five or six Fewer than three usually are not practicable because so much material accumulates that the analyst will have difficulty not to lose the thread The matter of fees is frankly discussed Analysts fees are as in the case of other physicians usually adjusted to the patients income But since each visit lasts from fifty to sixty minutes the number of patients an analyst can see in a day is of course much more limited than is the case with many other medical specialists Accordingly most analysts find it difficult to accept more than a very few patients at low fees This is unfortunate but unavoidable Endowed clinics where psychoanalysis can be practiced on patients of the lower income brackets are urgently needed Once the time and fee have been agreed upon it is expected that both patient and physician will abide by this agreement Some analysts charge their patients even when they do not come This has its good reasons but it is by no means an invariable rule

In order to put the patient at his ease he is usually asked to recline on a couch This has the double advantage of allowing the patient to relax and sparing him the embarrassment of constantly looking at the physician and being looked at by him A reclining position on a couch is not necessary to analysis but it is a great help where the method of free association is employed

From the start the patient is urged to talk freely about the things uppermost in his mind. He is at the same time constantly encouraged *to allow his mind to return to the events and feelings of his childhood.* When dreams begin to be recounted they are dealt with in relation to the patient's present life situation but they are used also to expose and reveal buried memories. Technical language is not used by the experienced analyst who usually *cautions his patient, at least in the earlier* phases of the treatment, not to read psychoanalytical treatises. Nor does he enter into theoretical discussions with him. He usually recognizes these discussions as a form of resistance.

The patient and his relatives are naturally greatly concerned as to how long the treatments will last. This is a *prediction not easy to make.* It depends upon a number of variable factors, not least important are the patient's willingness and capacity to change and the analyst's sensitiveness and skill. The treatment usually lasts a year, sometimes in stubborn and difficult cases much longer. Cure is not achieved necessarily as soon as the patient appears to have recovered, but the final proof of the pudding will be the eating. As Kubie put it[1] "... *it is fair* to measure results in terms of the patient's happiness and peace, his pleasure in activity, his freedom from disturbing states of depression, anxiety, guilt, fear or jealousy, and more particularly his freedom from the special neurotic symptoms which may have brought him to analysis."

CRITERIA FOR RECOMMENDING PSYCHOANALYSIS

Our criteria for recommending analysis in preference to other forms of psychotherapy still are not sufficiently sharp. Certain factors must always be taken into account. They are well summarized by Hendrick in his valuable book.[13] He lists among them age and general intelligence, strength of character and also what is called "secondary gain." This latter refers to those pleasures which a psychoneurotic person seeks to derive from or win by his symptoms or character traits. He states quite correctly that these pleasures are not the cause but rather the result of the illness. Hendrick finally emphasizes the importance of considering the real situation in which the patient finds himself. If this is too threatening or destructive to the patient and if he is caught by fate in a situation from which he cannot extricate himself, our efforts to help him by analysis probably will be thwarted. One would not attempt to analyze a starving, brutalized inmate of a prison camp no matter how neurotic he was.

Although such qualities as intelligence and strength of character may be judged on practical, experimential grounds, we now are in possession of certain methods which can give us a more quantitative appraisal of them Intelligence tests and projective techniques such as the Rorschach and the thematic apperception test of the clinical psychologists are proving of value in the selection of those patients suitable for analysis Sometime however, we need to resort to a trial period of a month or six weeks a kind of shakedown cruise, in which we explore the personality During such a period the negative factors in prognosis usually will become manifest and no harm is done to the patient

Results of Psychoanalysis

From what has been said it must be obvious why it is so difficult to estimate the results of analysis or to build up a body of significant and reliable statistics We are dealing with a subject in which the variables are incalculable not least among them being the skill, native ability and resourcefulness of the analyst himself even assuming him to have fulfilled all the stringent and necessary requirements of his training Still, for those demanding statistical evidence whatever their value, data can be found in the reports of the Berliner Psychoanalytisches Institut, of the London Clinic of Psychoanalysis and of the Institute for Psychoanalysis Chicago[14] The results obtained in private practice have never been adequately evaluated and summarized

There are many points still at issue between analysts In Freud s own words Psychoanalysis has never claimed to give a perfect theory of the human psychic life but has only demanded that its discoveries should be used for the completion and correction of knowledge we have gained elsewhere [15] It may, therefore be said that the psychoanalytic theory endeavors to explain two experiences which result in a striking and unexpected manner during the attempt to trace back the morbid symptoms of a neurotic to their source in his life-history, viz the facts of transference and of resistance Every investigation which recognizes these two facts and makes them the starting points of its work may call itself psychoanalysis even if it leads to other results than my own [16] The definition of what psychoanalysis is and what it is not should by now be clear, and there is no justification for using the term loosely or applying it where it does not belong The door is left open for further experimentation for efforts to shorten this often tedious and costly process for extending the field into psychotic and psychosomatic illness for com

biming it with hypnosis and the use of drugs It is the method which has value and which was Freud s great contribution because it has given us our first rational approach to the irrational Since this is true it is not surprising to find it becoming of increasing importance both to psychiatry and to clinical medicine

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CHAPTER XXXIV

HYSTERIA

BY F GOLLA

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HISTORICAL

The history of the disorder known as hysteria offers a striking example of the sterilizing influence that tradition may have upon thought In the

Hippocratic books the convulsive cries of women were ascribed to malposition of the uterus and labelled accordingly, and for nearly two thousand years the uncritical acceptance of authority hindered any progress being made in our knowledge of hysteria. In 1618 Lepois, a physician of Pont à Mousson, for the first time challenged the tradition of the uterine pathogenesis of hysteria and described similar symptoms in men and immature girls, and later in the seventeenth century his views were accepted by Sydenham and Willis. Sydenham taught that hysteria is not only common but shows itself under an infinity of different forms, and imitates nearly all the maladies to which the human race is subject. It was not, however, till Briquet in 1859 described hysteria as a "dynamic" affection of those portions of the brain that serve affective states and sensation that the modern study of hysteria began. His description was elaborated by Lasègue and Charcot, and his pupils conducted a systematic study of hysterical symptoms which, though it has added much to our knowledge, is also responsible for much that has delayed our arriving at a true conception of hysteria by reason of their attempt to constitute a clinical entity without due consideration of its etiology. The later work of Bernheim, Dejerine and Babinski has been devoted to the better defining of hysteria, and of the therapeutic measures that it necessitates.

Symptomatology of Hysteria

It has seemed preferable to attempt first a clinical description of hysterical symptoms, and later to discuss their pathogenesis, and to attempt a definition of hysteria from the objective point of view. A definition of what constitutes an hysterical symptom must, however, be premised, and we may tentatively adopt the view of Babinski and consider as hysterical symptoms all such disorders as cannot be shown to be due to organic lesions affecting the bodily mechanisms which it is possible to produce by volition or in response to suggestion, and which can be made to disappear by the influence of countersuggestion.

Disturbances of Sensation

Hysterical Anesthesia.—The occurrence of anesthesia as an hysterical symptom was altogether ignored by the older observers. There is no stronger testimony to the view that the hysterical symptom depends for its existence on the unconscious suggestion on the part of the investigator than the fact that its existence was not noted before 1846 in a letter from Gendrin to the Paris Academy of Medicine. Briquet in 1859 found hysterical anesthesia in eighty five per cent of his cases. Bernheim was the first to recognize the

purely psychical nature of hysterical anesthesia and his views speedily gained universal acceptance

Hysterical cutaneous anesthesia may affect all modes of sensation or be limited to certain sensations thus a loss of pain sensation may occur with preservation of tactile and thermal sensibility Its distribution may in very rare cases cover the entire body More frequently it involves one side of the body only and such hemianesthesia is often accompanied by a disturbance of the special senses on the homolateral side Occasionally one or more limbs or segments of limbs are involved such anesthesia usually terminates at a sharp line encircling the limb corresponding with one of the articulations knee or elbow hip joint or shoulder joint For this reason it is commonly spoken of as stocking or glove anesthesia Distribution in the shape of irregular patches is also found These patches generally subtend some viscus that is said to be painful and their distribution conforms neither to that of the segmental nor peripheral nerve areas of distribution There is reason to think that anesthesia is very rarely present until its possibility has been suggested to the patient by the process of examination The mere question as to whether a patient feels the prick of a pin carries with it the suggestion that he may possibly not feel it In a certain residuum of cases anesthesia is complained of spontaneously in a patient who has never been examined Here it may depend upon autosuggestion stimulated possibly by some accidental occurrence drawing the patient s attention to the part Anesthesia of the mucous surfaces is often found so much so that anesthesia of the pharynx has been regarded as a pathognomonic symptom of hysteria Equally with cutaneous anesthesia this symptom appears to be created by the method of examination Conjunctival anesthesia is of comparatively rare occurrence Anesthesia of the viscera is also occasionally noted Loss of muscle and joint sensation is quite common in limbs affected by hysterical paralysis

The diagnosis of hysterical anesthesia in a case where previous observation has suggested this symptom to the patient depends firstly on the elimination of signs of organic disease such as would account for its presence and it should here be noted that it is a not infrequent concomitant of true organic nervous lesions Secondly on its distribution which is frequently not of such a nature as would occur in an organic case Thirdly on the degree of loss of sensation A complete loss of all forms of sensation in the absence of a peripheral nerve lesion should lead to suspicions of its psychical origin Fourthly on the possibility of showing by confusional tests that the patient really feels of these the most striking is the ludicrous test of Janet The patient is instructed to shut his eyes and answer no every time he is touched but feels nothing Not all patients can be caught out in such a simple fashion I have often found that the psychogalvanic reflex of Veraguth gives

infallible results in such cases in which there is sufficient doubt as to justify the trouble of this method of verification since the reflex diminution of conductivity to a severe painful stimulus is entirely outside any voluntary control

Hyperesthesia.—All forms of hyperesthesia may be noted. Painful cutaneous areas are relatively rare except in the vicinity of an old injury. Painful joints and muscles are extremely common in hysteria and nearly invariably associated with hysterical paresis of the limb. Hyperesthesia of the viscera is so common that its occurrence on pressure in the ovarian region was long thought to be pathognomonic of hysteria. The diagnosis of the hysterical origin of these hyperesthesias is generally easily effected by noting their absence when the attention of the patient is directed elsewhere and the supposedly hyperesthetic area is secretly stimulated either by pressure or movement.

Subjective pain is frequently complained of and its distribution and nature are manifold. Its diagnosis as hysterical often presents very great difficulties and we are sometimes left in doubt as to whether we are not dealing with an exaggerated account of some real discomfort. The absence of signs of organic disease and the improbable nature and distribution of the pain are the chief elements in the diagnosis.

Disturbances of Special Senses

Disturbances of smell and taste are most frequently of the nature of total loss of these sensations and, like the cutaneous anesthesia, they generally are attributable to suggestion derived from clinical observation. The loss may be complete or attributed to the smell or taste of some particular substance only. It is of diagnostic importance that they are practically always first observed by the physician whereas an organic loss is generally complained of spontaneously by the patient. Loss of taste is usually associated with analgesia and anesthesia of the tongue. Hyperesthesia of smell and taste, always in the form of undue susceptibility to disagreeable tastes and odors, is occasionally complained of.

Visual Disturbances.—Hysterical loss of vision is usually complained of spontaneously by the patient. It may be present in all degrees from total amaurosis to mere dimness of vision. Total bilateral amaurosis usually occurs suddenly, not infrequently after an hysterical fit. The pupillary reaction to light is as a rule normal though not a few competent observers have reported the occurrence of hysterical amaurosis with non-reacting pupil. The number of such cases recorded has diminished suspiciously in recent years and probably many of the patients were suffering in reality from disseminated sclerosis or retrobulbar neuritis. The method of observation

of the propelling reflex is moreover an important factor. Oppenheim has shown that even non amaurotic hysterical eyes when tested by a flash lamp occasionally fail to react whilst the normal light reaction can be obtained in daylight. This anomaly he explains as due to the causation of fear with its concomitant pupillary dilation when a sudden strong light is flashed into the eye. No one of course would make a diagnosis of hysterical amaurosis without a preliminary ophthalmoscopic examination but even when the fundus oculi is normal the diagnosis occasionally presents difficulties. Disseminated sclerosis occasionally commences by the rapid development of complete bilateral amaurosis without any other symptom. The pupils in such cases may react normally and the ophthalmoscopic appearances be normal. The amaurosis after a short period disappears as rapidly as it came so that restoration of vision cannot be appealed to as a sign of its functional nature. I have seen a case of this nature in a young girl complaining of the sudden onset of amaurosis who had been considered to be hysterical by several of the most distinguished neurologists and ophthalmologists in London. After a month her vision returned. Some two months later the patient again complained of amaurosis and this time with symptoms of well marked disseminated sclerosis. When vision again returned some weeks later she was left with a central color scotoma and a patch of sclerotic atrophy had made its appearance in the optic disc of one eye. Since then years have passed and she is now a well marked case of disseminated sclerosis but has never had any return of the amaurosis. Contrary to the general impression it may be asserted that a case of hysterical amaurosis cannot always be detected by study of his behavior: he may actually walk into obstructions and refrain from flinching when a menacing movement is made towards the eye. As a rule however the hysterical blindness is not so profound but that tests of this nature reveal its nature. There is in addition a certain theatrical exaggeration of the difficulties of getting about which is absent in true blindness. The history of the onset is often of the greatest value in throwing light on the hysterical nature of the symptom. Blindness resulting from a bilateral lesion of the occipital lobes occurring without other symptoms is fortunately rare but may be very difficult to diagnose from hysteria. Unilateral amaurosis is of much more frequent occurrence. Its hysterical nature can readily be detected by the use of the apparatus of Fless, the patient looking at a card through two eye holes in a box in which by means of mirrors the visual directions have been crossed. Unaware of this he maintains that the side of the card which would normally be seen by the amaurotic eye but is in reality seen by the sound eye is invisible. Hysterical contraction of the visual fields is frequently found during examination of the patient by the perimeter. There is little doubt but that it is always the result of suggestion due to the process of examination. A patient

with only a minute central field moves about the room and avoids laterally placed objects in a perfectly normal fashion The hysterical contracted visual field unlike that due to organic lesions remains the same size when the distance of the eye from the center of the perimeter is varied just as if the patient were looking down a long tube Hemianopic contractions of the visual field and even central scotomata can be readily suggested by the observer in the course of a perimetric exploration In cases when there is any doubt the use of a prism so as to make correct orientations impossible on the part of the patient readily clears up the diagnosis Hysterical color blindness may be detected by the normal interpretation of color mixtures by the patient thus a patient who saw one of the complementary colors on a disc as white had a perception of gray when the disc was rotated Macropsia and micropsia are both occasionally complained of by the same patient micropsia when near objects are viewed and macropsia for distant object Hyperesthesia to light is by no means rare and injudicious treatment by dark glasses or eye shades makes this symptom very hard to remove

Hysterical Deafness —This may be total or partial Total hysterical deafness is not rare and its diagnosis frequently offers some difficulty It must be distinguished from a peripheral nerve deafness and from cortical deafness The absence of subjective signs of vestibular involvement and the normal response of nystagmus and giddiness when the patient is tested on the rotating chair is strong presumptive evidence against a peripheral nerve lesion Cortical deafness will usually be associated with sensory aphasia depending on loss of auditory word memory apart from the presence of other symptoms denoting a gross cerebral lesion Hysterical deafness is very difficult to detect from observation of the patient s conduct there i however one test which I have never known to fail and that is the Veraguth psychogalvanic reaction in response to startling loud noises Unilateral hysterical deafness can generally be detected by confusion methods such as whispering into the bell of a binaural stethoscope with the earpieces applied to the patient s ears and secretly blocking the tube leading to the sound ear

Vertigo is occasionally complained of in hysteria and in those rare cases in which the patient complains of a definite sense of rotation in one direction the diagnosis may be extremely difficult and depends on the failure to discover other symptoms of vestibular disease and the removal of the symptoms by suggestion

Disturbances of Motor System

Hysterical Paralysis —The hysterical paralyses like the organic forms may be classified as hemiplegias paraplegias and monoplegias The differential diagnosis between the hysterical paralysis and its organic equivalent

depend chiefly on the absence of such symptoms in the hysterical conditions as have been shown to invariably accompany an organic lesion and to a less extent on the presence of some positive characteristics of hysteria that are usually absent in organic paralysis The differential diagnosis has been systematized by Babinski and the following are some of the more important points (1) In organic hemiplegia the tendon and bone reflexes may be lost or diminished at the onset later they are almost always exaggerated and there is often ankle and patellar clonus In hysterical hemiplegia these reflexes show no change There is no ankle clonus (2) In organic hemiplegia the cutaneous reflexes are affected The abdominal and epigastric reflexes are lost on the side of the hemiplegia The plantar response is extensor on the hemiplegic side In hysterical hemiplegia the cutaneous reflexes are unaffected The plantar response is flexor (3) In organic hemiplegia the course is regular contracture succeeding flaccidity The paralysis shows no tendency to shortlived remissions or exacerbations In hysterical hemiplegia the paralysis may remain flaccid indefinitely or it may be spastic from the first The symptoms are liable to rapid remissions and exacerbations (4) In organic hemiplegia the paralysis is limited to one side of the body In hysterical hemiplegia it is not always so limited Facial paralysis when it occurs in hysteria has special characters of its own to which reference will presently be made (5) The paralysis affects movements which are accessory to voluntary movements but do not normally enter into the content of consciousness Thus when the organic hemiplegic attempts to rise from the position of dorsal decubitus without the aid of his arms owing to weakness of the extensor muscles of the hip on the hemiplegic side the leg is lifted off the ground and flexed at the hip joint In the hysterical hemiplegic when a like attempt is made both heels and legs remain firmly pressed on the bed as in the case of the normal individual (For many other points of differential diagnosis the reader may consult the memorable paper of Babinski Gazette des hopitaux 1900 LXIII 5 1)

It is well to bear in mind that in the case of an organic hemiplegia that has nearly recovered the deep and superficial reflexes may have become normal whilst there is still some degree of hemiplegic weakness The differential diagnosis between organic and functional paraplegia will depend on the presence of a bilateral modification of the reflexes similar to that described in organic hemiplegia An exaggeration of the reflexes of defense may occur in the organic case such as the dorsal flexion of the foot when the skin of the dorsum of the foot is vigorously pinched—a reflex that will in hysteria only be evoked by stimulation of the plantar surface of the foot The occurrence of incontinence of urine is pathogonomonic of organic disease Trophic cutaneous changes such as bedsores are invariably absent in hysteria When the paraplegia is due to involvement of the motor

nerves of the gray matter of the anterior cornua amyotrophy with reaction of degeneration will be present

An hysterical monoplegia can as a rule be fairly easily distinguished from one of organic origin Often the history of the onset sufficiently indicates the hysterical nature of the case as when it purports to follow such a traumatism of the limb as could not possibly have involved the nerves supplying it In organic monoplegia some muscles are generally less affected than others whereas in an hysterical monoplegia all the muscles of the affected area are absolutely paralyzed Amyotrophy with alterations of faradic excitability and alteration of the deep reflexes are absent in the hysteric A stocking anesthesia corresponding in its extent with the limits of the paralysis is usually found in the hysteric—but never the segmental or peripheral type of anesthesia that may accompany an organic lesion When the hysterical monoplegic limb is raised by the observer and suddenly released an appreciable interval often occurs before it falls and on manipulation of the limb a sense of resistance or on the other hand of assistance is occasionally encountered

Facial paralysis as a variety of hysterical paralysis deserves special mention It is almost always limited to the facial muscles innervated by the lower division of the seventh nerve and is unilateral Its hysterical nature may be demonstrated by the fact that the apparently paralyzed facial muscles will take part in many movements which require their cooperation thus an hysteric with apparent facial paralysis can blow out a candle a feat which obviously involves cooperation of the pseudo paralyzed half of the face *Hysterical ptosis* is most frequently bilateral When the patient is asked to open his eyes the ptosis becomes accentuated there is never the wrinkling of the forehead that occurs when the organic patient attempts to overcome his ptosis The eyebrow is drawn down on the side of unilateral hysterical ptosis while in organic cases it is almost always raised higher than on the sound side

Hysterical Contracture and Spasm —Hysterical contracture occurs very frequently after slight wounds to the extremities The onset may be within a few seconds of the receipt of the injury or after a lengthy period It is primarily a defensive reaction to avoid pain from the injury but persists in a remarkable fashion for almost an indefinite time after the injury has been healed Many observers including Babinski have regarded such contractures as reflex from irritation of the wound and considered that the fact that they did not in the late stages relax under anesthesia is a proof of their organic nature The permanency of the contracture under anesthesia and its resistance to suggestive treatment is as I pointed out in 1917 no proof of its organic origin It is due to change in the muscle taking place after a lengthy period of contracted immobility and may be exactly paralleled in

the tonically contracted muscle of local tetanus which after a sufficient length of time remains contracted after severance from the central nervous system or even after excision from the body The subsequent observations of Roussy and others have placed it beyond doubt that the contractures of this nature occurring in the war and termed reflex were really of functional origin and were if treated early removable by countersuggestion The absence of a history of initial short painful spasmodic contractions sufficiently differentiates them from local tetanus Similar hysterical contractures can occur without the primary suggestive factor of a wound Hysterical contractures are closely allied to the condition known as hysterical catalepsy This symptom generally occurs while in a state of stupor and may be associated with flexibilitas cerea the limbs remaining in any position in which they are placed by the observer Hysterical catalepsy differs from the catatonic states of dementia in that the hysteric more frequently assumes abnormal attitudes without being placed in them by the observer and is hence sometimes spoken of as pseudoflexibilitas cerea this distinction is not however an absolute one *Hysterical torticollis is of frequent occurrence* It is never dependent on the contraction of an isolated muscle such as may occur from an irritative lesion

Spasm of the facial muscles on one side is frequently associated with a spasmodic deviation of the tongue to the same side It is relaxed during sleep—a sufficient differentiation from the posthemiplegic organic facial contracture in which the tongue is deviated towards the uncontracted side of the face More rarely spasmodic contraction of the eye muscles is observed the most frequent form being a convergent spasm This is rarely kept up for any length of time and only occurs under observation Blepharospasm is common in children and markedly increased by receiving injudicious attention from the parent

The relation of the spasmodic contractures known as tics to hysteria is obscure Brissaud and Meige have shown that quite a number of tics have a psychical origin At the same time their resistance to countersuggestion their obviously agonizing nature and the absence of the psychical and physical symptoms of hysteria appear to indicate that they are due to a nervous *derangement other than that concomitant with admitted hysterical symptoms* On the other hand tics may occur in patients exhibiting many of the accepted hysterical symptoms and yielding readily to countersuggestion Our knowledge of the relation of hysteria to professional cramp is in the same unsatisfactory state

Hysterical tremor is a common symptom and in its frequency and range may counterfeit all the forms of tremor appertaining to organic nerve lesion Its obvious relation to the attention devoted to it by the patient generally suffices to reveal its hysterical nature

Extreme Asthenia.—Excessive fatiguability of the muscles is often complained of by the hysteric. Unfortunately the serious organic disease of myasthenia gravis is sometimes mistaken in its early phases for hysteria. In this disease the predominance of the symptoms in muscles innervated by the cranial nerves, *e g*, fatigue of the masticatory muscles, diplopia due to fatigue asthenia of the eye muscles, the heavy expressionless face with some degree of ptosis will generally furnish a key to the correct diagnosis. The fatiguability of the hysterical muscle to faradic stimulation will of course not differ from the normal in contrast to the myasthenic reaction of easy fatiguability.

Hysterical Pseudotetany.—A number of cases closely imitating tetany have been described as hysterical pseudotetany. Inasmuch as most of these cases have shown the Trousseau phenomenon and electrical hyperexcitability of the nerves, the fact that the tetanoid spasm disappears with suggestive treatment does not definitely establish its purely hysterical nature. Cases of true tetany with all the classical symptoms can be occasionally precipitated into the tetanoid spasm by a psychical stimulus. It would therefore appear to be probable that the so called hysterical tetany represents a mild form of tetany in which by an effort of the will the symptom can be inhibited.

Hysterical scoliosis is of two types. The one depends upon a primary contracture of the spinal muscles, the other on a contracture of the hip musculature which causes the pelvis to be tilted in an exaggerated form of the position in which it is when all the weight is put on one leg. The characteristic hip and shoulder correction of an organic scoliosis is absent in the hysterical type. Kyphosis and rigidity of the spine simulating spondylitis deformans also occur as hysterical symptoms.

Hysterical Incoordination.—All types of incoordination may occur in hysteria from the dramatic exhibitions of astasia abasia to stammering and slight intention tremor. The hysterical astasia abasia in which the patient professes inability to either walk or stand without assistance conveys more than any other hysterical symptom the essentially theatrical character. The patient who has been found on examination to present no symptoms of organic paralysis when attempting to stand flounders about, throwing out arms and legs wildly, performing feats of equilibrium in fantastic positions that would tax the ingenuity of a trained acrobat and finally falls without causing himself any injury and skillfully avoiding any object that might hurt him. If it were not for experience to the contrary it might well seem impossible to believe that any trained medical man could entertain a doubt as to the nature of the performance. All degrees of hysterical impairment of gait may be observed down to a slight limp. A careful preliminary examination seldom leaves any doubt as to their nature.

The Hysterical Seizure

The hysterical fit or seizure gains in elaboration in exact proportion to the amount of clinical attention that it secures. The major fits described by Charcot and Richer with their four stages of epileptoid convulsions, clownism, emotional attitudes and delirium are never seen in clinics where the manifestations are discouraged as soon as their hysterical nature is established. The motor symptoms have no particular sequence in development and are loosely and unsystematically constructed variations on a theme of clonic movements, tonic spasms, wild throwing about of the arms and legs, emotional attitudes and cataleptic rigidity. As in astasia abasia the impression of a clumsy attempt to deceive predominates in the mind of the observer in the majority of cases. Only occasionally is the hysterical attack presented with sufficient conviction to cause hesitation in the diagnosis between hysteria and epilepsy. The hysteric never injures himself in his fit, never bites his tongue, never passes water, the attack can generally be inhibited by a sufficiently severe stimulus and the conjunctival reflexes are never abolished. Epilepsy is, however, of all diseases the most easy to counterfeit once the actor has a good model. There are many recorded cases where malingerers have obtained admittance to epileptic colonies and succeeded in passing as epileptic for years under the eyes of skillful observers (Lewandowsky). For this reason the hysterical fits exhibited by patients who are inmates of a hospital for nervous diseases may be singularly convincing. The epileptic is not infrequently also an hysteric and in the absence of a genuine crisis, possibly scared by real or imaginary prodromal symptoms, he will often give an hysterical pseudoepileptic display. The excitement of the hysterical crisis may in the epileptic sometimes induce the supervention of a real fit. If these points were better appreciated we should hear less of attempts to trace a psychogenic origin for epileptic fits.

Disturbances of the Vegetative Nervous System

Hysterical symptoms referable to the vegetative nervous system (sympathetic and parasympathetic systems) might at first sight be thought to involve a contradiction of the definition of an hysterical symptom inasmuch as the vegetative nervous system is not under direct voluntary control. The fallacious nature of this objection will become more apparent when the pathology of hysteria is discussed; in the meantime it is sufficient to say that there is no voluntary action without a concomitant activity of the vegetative nervous system and if we are to apply the test of the efficacy of countersuggestion it must be to the volitional state that has brought about the

neural discharge of the vegetative nervous system and not to the discharge itself We cannot suggest to a patient that he is not to blush but we may suggest that he cease to think of the subject that causes blushing It is neglect of this extension of voluntary to involuntary nervous action that has caused Babinski and his school to eliminate from the category of hysteria many symptoms that properly belong to it

Pupillary Disturbances —A few people are able to contract and dilate the pupil at will We are therefore prepared to find myosis or mydriasis as a rare symptom in hysteria although many such cases have really been due to surreptitious instillation of drugs The loss of the light reaction during hysterical seizures has been attested by Westphal Karplus Hoche Bumke and many other observers so that difficult as it may be to account for it this symptom can not be appealed to in the differential diagnosis of hysteria from epilepsy Hysterical accommodation spasm with or without convergent spasm of the eyeballs also occurs

Secretory Disturbances —Profuse sweating either local or universal occasionally accompanies other hysterical manifestations Lacrimation without affective stimulus is a rare symptom Hypersecretion of the nasal mucosa in hysterical patients who are continually blowing the nose may be reckoned either as an hysterical symptom or as due to excessive stimulation of the mucosa One of my patients collected two pints of a glairy mucus containing fluid in twenty four hours Excessive salivation or absence of salivation are both fairly common symptoms

Cardiac Disturbances —Nervous tachycardia is far more often an accompaniment of the group of neuroses allied to hyperthyroidism than of hysteria I have never found it in uncomplicated cases of hysteria except as a very transitory phenomenon such as may occur in normal people on examination Subjective cardiac symptoms such as sensations of pressure and pseudo angina are of course common

Vasomotor disturbances are uncommon when uncomplicated by postural symptoms I can by no means confirm the observations of di Gaspero that psychical stimuli fail to evoke a vasomotor response in the hysterically monoplegic and anesthetic arm on the other hand the vascular response to psychical stimuli is universally depressed in hysteria Acrocyanosis as might be expected is a common accompaniment of hysterical paralysis The occurrence of hysterical edema once considered to be of great frequency is now generally doubted Edema of a monoplegic limb is however by no means rare but may be considered to be a sequel to the circulatory stagnation due to immobility Erythematous patches have been described on good authority as occurring in areas where the hysteric complains of painful paresthesia There is a certain amount of physiological evidence that when attention is drawn to a particular area of the skin a slight reflex vasodilation

of that area occurs accompanied by hyperthermia If this be true there are no a priori grounds for disbelief in the occurrence of patches of hyperemia as an hysterical symptom the evidence adduced rests however chiefly on old observations under circumstances that do not exclude fraud on the part of the patient

Visceral Disturbances —Esophageal spasm causing inability to swallow and probably accounting for the well known globus hystericus is a very frequent symptom Nervous dyspepsia undoubtedly is of frequent occurrence Our knowledge of the influence of psychical stimuli on the secretion of gastric juice would induce us to expect that hysterical aversion to food may lead to impairment of gastric secretion Anorexia nervosa has been considered by many writers to be a clinical entity associated with definite organic changes and not of an hysterical nature However this may be anorexia is certainly also an hysterical symptom and may be pushed to extreme limits The converse condition also obtains when the patient expresses an incessant desire for food and complains of gastric pain and discomfort when it is not gratified In such cases evidence may be obtained of gastric hypersecretion which when unneutralized by food will give rise to gastralgia The regurgitation of the gastric contents may occur in all forms from the simple vomiting of food to the eructation of gas and gastric secretions Hysterical vomiting may be very persistent and occasionally reduces the patient to an extreme degree of inanition Voluntary distention of the stomach by air swallowing is often an obstinate hysterical symptom and such patients often succeed in producing an enormous degree of abdominal distention All forms of hysterical intestinal disturbances have been noted from increased peristaltic action giving rise to true diarrhea to extreme degrees of constipation Much more common than true diarrhea is an incessant desire to go to stool accompanied with only very small hard evacuations thickly coated with mucus The hysterical nature of this type of mucous colitis has long been recognized but its differential diagnosis from the organic disease is by no means easy and must rest to a great extent on observation of the attitude of the patient toward his symptoms The origin of the so called hysterical tympanites is obscure it has been considered by some writers to depend on aerophagy It appears to have generally been present in cases of imaginary pregnancy occurring in hysterical subjects

Disturbances of micturition either take the form of retention or increased frequency of micturition Incontinence of urine is never an hysterical symptom though it is not unknown as a form of malingering

Bronchial asthma is by no means infrequent as an hysterical symptom its hysterical nature can only be established in any given case by careful consideration of the psychological concomitants and the nature of the stim

ulus that precipitates an attack Once asthma of hysterical origin has been established it by no means follows that it will yield readily to suggestion A case is on record of a well known German lung specialist and his assistant who for experimental purposes acquired the knack of reproducing a typical asthmatical attack After a time however they lost control over the asthmatical manifestation which began to appear uninvited and both became confirmed asthmatics

The male sexual apparatus is seldom affected in hysteria in other form than impotentia coeundi there is never hyperexcitability In the female sexual frigidity and anesthesia are common vaginal spasm without erotic concomitant may impede sexual connection

The possibility of the occurrence of *hysterical fever* has been much debated Whilst there is no doubt that psychical excitement influences the course of febrile temperature yet in view of the fluctuations of temperature that occur in the normal subject the evidence for the existence of hysterical fever is unsatisfactory

The Relation of Fraud to Hysteria

Between simulation and hysteria there is according to Babinski only a moral difference The difficulty cannot be thus easily laid To introduce the criterion of a moral difference is only to resuscitate the whole question in the form of an enquiry into the psychology of belief If we are to hold to the purely objective study of conduct which with all its limitations is at any rate the safe road in medicine such an enquiry is not open to us As a purely objective criterion we may however distinguish between those manifestations which are so self evident to the patient that he does not trouble to reinforce the demonstration of their specific nature by any auxiliary activity and those which he can only demonstrate to others by the employment of activities which not only form no essential part of the symptom complained of but whose very nature implies a logical denial of the existence of the symptoms These latter manifestations we commonly regard as fraudulent By the adoption of some such criterion as this we are enabled to avoid the problem of how much a patient believes in any given symptom—a question that is unanswerable in the present state of our knowledge Between the immediate actuality of the simple hysterical symptom and the complex construction of fraudulent symptoms there appears to be no hard and fast line An hysterical patient complaining of paralysis and suppression of urine will support the latter claim by means of a secreted receptacle which he empties surreptitiously Production of factitious skin lesions the use of the hot water bottle or friction to raise the temperature

of the thermometer and countless other forms of fraud have been described in hysteria

THE PSYCHICAL SYMPTOMS OF HYSTERIA

To attempt a logical division of hysterical symptoms into bodily and psychical symptoms is of necessity an unsatisfactory procedure involving much repetition Thus the mutism and deafness of hysteria considered as psychical symptoms are properly negative hallucinations and the motor paralysis a delusion of asthenia It is however not only more convenient but leads to a better understanding of these hysterical symptoms to consider them in terms of their bodily representation Certain other symptoms however occur without obvious bodily concomitants In investigating these psychical symptoms the same attitude must be preserved by the physician as that which he adopts towards the physical manifestations It makes little difference whether an hysteric tells us that he is unable to move his limbs or that he has lost all memory of certain events the fundamental mechanism is much the same In the latter case however there is much greater difficulty in determining to what extent the patient is dominated by the neurosis There is always a certain degree of resistance to the suggestion of a physical symptom but this resistance is minimal when we are dealing with psychical symptoms The patient is then infinitely more suggestible and the intangible nature of his subjective utterances deprives him of the necessary standard that enables him to present his physical symptoms as a consistent whole

Hysterical amnesia is a retrograde amnesia for events which have either in themselves been unpleasant or have unpleasant associations In certain rare cases the patient spontaneously professes a complete loss of memory of a period which may cover days or even years The rarity of this condition in the hysteria of civil life is in striking contrast to its alleged frequency during the war There is of course no absolute test of the existence of amnesia other than the patient s assertions In some enquiries conducted at a military hospital I was however able to ascertain from collateral evidence and in some cases from the patient s confessions to his comrades that at any rate a number of these cases of amnesia were really fraudulent productions by malingerers There is no doubt that a retrograde amnesia may follow an organic brain lesion such as is caused by concussion Such organic amnesias were not infrequent in the war and on account of their nature attracted a good deal of attention from the lay press they offered therefore a source of suggestion to the hysteric and by its acceptance cumulative reinforcement of the suggestion occurred in others till in some neurological hospitals there appears to have been a regular epidemic of amnesia Turning

now to the amnesia which is discovered only in the course of examination of the patient it may be observed that like all hysterical symptoms its development depends greatly on the suggestions unconsciously conveyed by the physician When a patient professes amnesia of some disagreeable event any attempt to probe the extent of his amnesia acts as a direct suggestion that he cannot remember and the further the investigation is pushed the more complete and extensive will be the amnesia it is the old story of the production of hysterical anesthesia by the investigator's pin

Stuporous states with pseudocatatonic symptoms are occasionally to be met with If the observer be unacquainted with the previous history of the patient such cases are easily mistaken for dementia praecox but do not show a like independence of the presence of a witness

Many hysterics have a tendency to indulge in autistic thinking They find relief from the disappointments and conflicts of daily life in the construction of day-dreams Such a process is very common in childhood and most adults can recall periods when as children they lived almost more in these day dreams than in their actual life The hysteric as we shall see later is characterized by a tendency to adopt any form of expression that will act as a substitute for the organic resonance of normal emotion Autistic thinking is not it is true primarily adopted as a mode of expression but rather as a means of forgetting a situation in which the patient is in conflict with his environment Ultimately however the enactment of these day dreams suggests itself as a convenient symbol to convey mental distress in addition to the bodily symptoms under the fostering care of an interested physician they may be elaborated to any extent and be presented not as a process of autistic thinking but by a dramatic representation of it The introduction of the dramatic personality is generally effected by a curtain raising device known as going into a trance That there is ever a complete loss of the continuity of aims and interests that we include under personality is doubtful Just as it is impossible to induce a young girl in a hypnotic trance to strip herself before a mixed audience though she is perfectly ready to go through a dramatic representation of murder with a paper knife so it is equally difficult to discern any genuine antagonism between the multiple personalities of the hysteric If the perseveration of such conditions were considered to be a reproach to the therapeutic skill of the physician we should probably hear no more of them than we do nowadays of the Hysteria Major of the Salpetriere

Pathology

The foregoing pages have been devoted to a brief review of the principal symptoms of hysteria It is now necessary to attempt to formulate the

nature of the disturbance that gives rise to them It must be frankly admitted that our knowledge is far too incomplete to admit of any account of the mental states of the hysteric that would be sufficiently acceptable to prove useful The mass of contradictory views on hysteria lends color to Lasegue s dictum "The definition of hysteria has never been given and probably never will be Much of the chaotic condition of thought on this subject results from an attempt to study the psychology of the neuroses from a subjective rather than a purely objective point of view The physician as Mercier has pointed out is concerned with disorders of conduct—of disorders of mind we know nothing and an attempt to formulate them can only be accomplished by what Avernarius has termed the process of introjection" leading to the substitution of symbols which we term ideas and mental states for the concrete actualities of experience and like all symbols these only partially correspond to the material which they symbolize The methodological problem is very similar to that which confronts any attempt to study the psychology of the lower animals—here it is only by a rigid exclusion of all anthropomorphic introjection" that progress has been made and an attempt to study hysteria in terms of conduct or behavior would appear in the present state of our knowledge to be the most promising method for the medical man This method it is true cannot furnish more than an objective account of the problem teleological significance can not be expressed nor can desire or conation properly be discussed but it at least has the merit of making it possible to represent hysteria as a clinical entity in terms of behavior Within these limitations we may enquire into the common properties of the symptoms of hysteria and thence attempt to deduce their origin

For a disturbance of nervous activity to be considered to be hysterical it is in the first place necessary that it should be clearly distinguished from the manifestation of an organic lesion of the central nervous system Bernheim long ago pointed out that all the symptoms of hysteria were such as might be produced by hypnotic suggestion and Babinski amplified this view by pointing out not only that hysterical symptoms are such as might be caused by suggestion but that they actually can be removed by counter suggestion To quote Babinski s own words Hysteria is a pathological state manifested by disorders which it is possible to reproduce exactly by suggestion in certain subjects and can be made to disappear by the influence of persuasion (counter suggestion) alone " This definition of Babinski s has been received with almost universal assent Its acceptance without committing us to any theory of the psychology of hysteria allows us to determine the clinical entity to which this label can be affixed It implies however that hysteria can only manifest itself through mechanisms that are normally under volitional control and an attempt has been made by Babin

ski and his followers to purge the syndrome of hysteria of all symptoms that are not directly under the control of the will This attempt has resulted in many errors of which the most glaring was the relegation of late hysterical contracture to the position of a reflex contracture set up by irritation of the wound owing to its not being directly curable by countersuggestion and the contractured muscle showing certain abnormalities to electrical stimulation and not being completely relaxed under anesthesia It is now generally admitted that the persistence of the contracture when volition has been abolished by anesthesia is due to a change of a degenerative nature taking place in the muscle whose normal metabolism and lymph supply has been interfered with by the persistent hysterical contraction Such errors are bound to creep in when an attempt is made to delimit the power of the brain to effect bodily changes—thus when an unpleasant thought is voluntarily recalled it may be accompanied by some such emotional concomitant as blushing and a voluntary act is here manifested by an involuntary mechanism Such difficulties need not however affect the truth of Babinski s definition though they impose a certain elasticity in its application Granted then that the hysterical syndrome consists in the manifestation of symptoms analogous to those that might be caused by suggestion are they a manifestation of some structural nervous derangement or are they the expression of a special method of psychical activity in an otherwise normal individual? Charcot and Pitres regarded the presence of certain stigmata as pathognomonic of the hysterical state they believed them to be of a permanent nature and to be present without the patient s knowledge Amongst these stigmata are anesthesia of the pharynx general hemianesthesia unilateral diminution of the acuity of the special senses especially vision and the presence of various hyperesthetic areas One and all of these supposed stigmata have been shown to be the results of unconscious suggestion on the part of the physician They only appear when sought for and hence suggested Thus to prick a patient with a pin and to ask him if he feels it is in itself to suggest to the patient that he may be anesthetic Apart from these evidences of suggestibility an hysterical patient shows no constant symptom on physical examination such as would constitute hysteria a morbid entity The age at which hysteria is most common suggests that its manifestations are in the main coincident with the period when the stress of the external world bears most heavily on the nervous organism which has not yet established habitual reactions The following table is that of Kraepelin

PERCENTAGE AGE INCIDENCE OF COMMENCEMENT OF SYMPTOMS

10th year	15th year	20th year	25th year	35th year	40th year	45th year	50th year
0 9%	2 1%	36 3%	1- 1%	6 3%	4 4%	1 9%	1%

An evaluation of the psychology of the hysterical individual presents very considerable difficulties The problem is to discover whether the clinical entity is an expression of a pathological nervous state and it is only too easy to confuse the symptoms that the patient exhibits (because he has hysteria) with those that might indicate an hysterical diathesis Most psychological investigations of hysterics fail on account of this difficulty It is not from the specialist who sees the patient in full possession of his malady but from the general practitioner or an intelligent schoolmaster who has known him most of his life that we may expect the most valuable evidence On one point all evidence seems to agree and that is the flimsy effect communicated by the hysteric character The potential hysteric lacks self reliance he leans on others he is eminently suggestible Morally he rarely shows any abnormality beyond a certain degree of slyness and untruthfulness I have never found any sexual hyperexcitability and the opinion of most neurologists who are not obsessed with Freudian theories is that his amativeness is rather below that of the normal individual His egotism is usually pronounced of friends he has few and he is rarely industrious Beyond such generalities it is difficult to go nor can they either singly or together be built into a well defined hysterical diathesis A neuropathic family history can be obtained in a very large number of cases but the proportion would not appear to furnish conclusive evidence of hereditary instability being a very potent factor in hysteria When we enquire into the determining cause of the onset of hysteria we find little to help us It is beside the purpose at this stage to discuss the various views that have been put forward as to the nature of the initial stimulus that precipitates the patient down the hysterical path unless it can be shown that it is of a nature inevitably leading to hysteria and this is obviously absurd All are in agreement that the situation that precipitates hysteria is one where the patient finds himself in more or less acute antagonism to his environment that is a disagreeable situation There is little evidence that an acute emotion can per se give rise to hysteria it is only when the circumstances giving rise to the emotion are in continual conflict with the activity of the patient that hysteria arises In the war the cases of hysteria diagnosed under the silly term shell shock all arose after the concussed patient had left the line and when the prospect of return was in direct conflict with his shattered resolution No one suggests that the hysteric has undergone experiences that are not common to the majority of mankind and we are concerned to know why he reacts in a different fashion to the normal man So far the objective method fails to give a key to hysteria the patient is not superficially different from other individuals somewhat egocentric and deficient in self reliance nor has he suffered psychical traumata which many of them have not undergone with impunity If however we study the mech

anism of the hysterical syndrome we may obtain some clue as to its origin The essential characteristic of the hysterical symptoms is the unconvincing manner in which they are present they never seem to pervade the whole personality of the patient but are indicated by him in an objective fashion Various observers have interpreted this characteristic as evidencing dissociation of the personality or manifestations of the unconscious In everyday language we have another name for the type of behavior we call it theatrical And it may be noted that a dramatic performance involves some such dissociation as has been attributed to hysteria—it is only the greatest artists who become so incarnated in their parts that they lose consciousness of the ego that applauds and criticizes their dramatic utterances and the hysteric is not of the stuff of which great artists are made Babinski has said that between the manifestations of fraud and those of the hysteric there is only a moral difference it might be said that in hysteria the actor shows all degrees of absorption in his part But granting that hysteria is a dramatization of an internal conflict in terms of pseudo-pathological symptoms how comes the patient ever to adopt this medium of expression? To answer this question we must consider how a normal person responds to an emotional stimulus All emotion is accompanied by bodily changes Alterations of respiration of the rhythm and force of the heart, of vascular visceral and muscular tonus constitute the bodily changes which are felt as emotion and the bodily response varies according to the nature of the stimulus The experience of this organic resonance following on the perception of an exciting fact is the preponderant factor in the mental state of fear love or hatred that we term emotion As put by James "If we fancy some strong emotion and then try to abstract from it all the feelings of its bodily symptoms we find we have nothing left behind There can be little doubt but that this is an overstatement James s theory of emotion ignores the essential relation of the circumstances which produce emotion to preexisting conative tendencies but it is indisputable that the organic changes constitute a potent factor in the emotional response to a stimulus Whatever be our view of the causal relation of these bodily changes to the basic mental state evolved by an emotional stimulus it must be conceded that their nature and intensity profoundly influence the specific affective tone of an emotion Now in the hysteric there appears to be good reason to believe that the bodily changes accompanying emotion are abnormal In 1918 I published at a meeting of the British Medical Association some observations on the response of the hysteric to emotional stimuli by the well known psychogalvanic reaction of Veraguth I found in all cases that the emotive reaction was markedly depressed and these observations were subsequently confirmed by Professor Waller The reaction consists in a diminution of the resistance of the skin to the passage of an electrical current in response to

any stimulus that normally causes emotion This reaction is not directly influenced by any effort on the part of the subject and constitutes an ideal objective method of quantitatively determining whether a given stimulu be it a physical or a mental one has caused an emotional reaction Painful thoughts the feelings of shame and anger are all registered faithfully by the galvanometer When however we attempt to dramatize an emotion by reciting emotional poetry trying to laugh or cry or work ourselves into a fictitious rage however perfect the dramatic rendering may be the galvanometer needle remains steady showing that at least one bodily concomitant of emotion is absent If now an hysteric be examined precisely the same thing happens though the patient appears to be suffering extreme emotion the galvanometer gives him the lie In one of my cases a young hysteric evolved the memory of his dead brother tears ran down his cheeks and he lamented in the language of a South London melodrama that he had not been taken and his dear brother left to comfort his poor old father yet all the time the galvanometer which will respond to the slightest passing regret or vexation of a normal person said nothing Not only are the hysterical displays void of this emotional factor but the patient does not respond or only to a minimal extent to stimuli whether painful or pleasurable that would produce normally intense reactions It would be assuming too much in our ignorance of the affective concomitants of this particular reaction to say that the hysteric practically feels no emotion but we are entitled to assume that he feels it in a very different way to the normal individual inasmuch as important bodily reactions are absent Experiments with the plethysmograph and pneumograph have given me much the same results though less decisively—the emotional reaction of the hysteric is subnormal If now we consider the position of a man incapable of adequate emotional reaction with its after effect of relief in the presence of a distressing situation we obtain some clue a to the genesis of the hysterical syndrome The patient knows that his situation is in conflict with hi interests it may be dangerous as in war it may merely be the irksomeness of discipline or domestic duty and he is unable to express it by the internal language of the emotions And yet expression or in other words a motor response to the stimulus is a physiological necessity he attempts then to express himself by a dramatic representation of the situation in terms not of the specific internal physical discomfort that we term a disagreeable emotion but in some other bodily manifestation which we are accustomed to associate with suffering The process is not as a rule a conscious one in a very superficial form it occurs now and again in the course of the lives of most normal people—during periods of much worry and annoyance not perhaps of great emotional import we occasionally ma surprise ourselves laying stress on minor ailments and sensation of fatigue which we adduce in evidence of the intol

erable manner in which the situation is affecting our well being The more completely the process of dramatization occupies the ego the less room does there appear to be for its conscious appreciation thus we have all degrees of hysteria from those which are hardly distinguishable from clumsy fraud to the entire absorption in the part exhibited in the amnesic condition and the hysterical fugue Every special kind of emotion to quote Professor Stout essentially involves a characteristic end or direction of activity mental or bodily anger tends to destroy or disable its object fear to avoid or evade it These substituted dramatizations of the hysteric likewise exhibit a tendency to accomplish the same end as would be served by the emotion those associated with fear or discomfort are obviously the most frequently observed but when brought to bay the patient may give a highly theatrical display of anger or resentment the fatuity of which is patent to the most superficial observer The symptoms which first served as a language for the expression of conflict assume in their own right an ever growing source of interest for the hysteric reinforced by the extraneous sympathy and minor sources of comfort which they may evoke They possess an additional attraction in that the concentration of attention directed to them makes it easier to ignore the memories of the unpleasant experiences in which they originated In an objective study of conduct there is little room for the theory of the dynamic value of the repressed complex on which so much stress is laid by many psychotherapists but the appeal to motor manifestations as adjuvants to the suppression of painful memories rests upon a sound basis of observation dating from the work of French neurologists on the pathogenesis of tics

Treatment

In the foregoing attempt to reconstruct hysteria from the purely objective point of view it will be noted that the hysteric is considered as a person whose emotive reactions are different to those of the normal individual That this is so during the period that the patient comes under observation as exhibiting hysterical symptoms and for at any rate a considerable length of time afterwards is demonstrated by the observations on the psychogalvanic reflex That this abnormality of reaction is constitutional and precedes the hysterical attack is probable From such evidence as can be gathered by personal observations and from the accounts of friends it usually appears that the hysteric throughout his life has always been deficient in self reliance egocentric highly suggestible and prone to complain of imaginary ailments It is not hard to reconcile these features especially suggestibility with the imperfect grip of reality attributable to a deficient

organic resonance to affective stimuli. The suggestibility of the hysteric is indeed a factor that proves a stumbling block in an attempt to evaluate the efficiency of any particular method of treatment. Lacking the directive force of normal emotional tone the patient is receptive of any suggestion whether autogenous or exogenous that will offer a facile path for the nervous process seeking expression. The hysterical symptoms can usually be removed or substituted by any process of suggestion no matter how irrational suggestions no matter how grotesque as to the nature of the initial complex are easily accepted and endorsed by the patient. These facts long familiar to all neurologists from the thorough and objective observations of such workers as Bernheim Janet and Babinski have recently been to a great extent lost sight of in England. The enormous number of cases of neuroses in the war and the weakness and inaptitude of the guiding authority frequently led to the treatment of hysteria falling into the hands of men for the most part innocent of a neurological training. Astonished at the facility with which hysterical symptoms could be made to disappear by some particular form of suggestion and unaware that for years it has been a truism among neurologists that any form of suggestive treatment may abolish a given symptom some of these workers were persuaded that the abolition of a particular train of symptoms meant the recovery of the patient and boldly announced the performance of ten minute cures ignoring the neurotic substratum of which the symptoms are but outward signs. Their method have often been surpassed both in swiftness and dramatic eclat by Dr Bodie and other performers on the music hall stage. Others again ignoring the facility with which the hysteric can be led to acquiesce in all suggestions have disinterred by psychoanalytic methods repressed complexes often of a sexual nature and pointed to the cures following on suggestive treatment based on the revelation of the true nature of the complex as a proof of its causal reality. It cannot be too strongly urged that the removal of hysterical symptoms proves nothing beyond the suggestibility of the patient. In no department of medical work is such a high degree of intellectual honesty and scientific acumen necessary to the physician. It should be self evident that a sound knowledge of organic disease is also a necessity but unhappily the psychotherapist is all too frequently destitute of this essential and it is becoming an experience of alarming frequency to find serious organic disease treated as a functional neurosis. The recognition of the hysterical element as a concomitant to organic symptoms has been tardy and again involves a sound knowledge of the pathological physiology of the nervous system. Briefly no psychological training however profound can justify an attempt to treat hysteria in the absence of a thorough knowledge of organic neurology.

In treating a case of hysteria we have to deal not with a normal nervou

erable manner in which the situation is affecting our well being The more completely the process of dramatization occupies the ego the less room does there appear to be for its conscious appreciation thus we have all degrees of hysteria from those which are hardly distinguishable from clumsy fraud to the entire absorption in the part exhibited in the amnesic condition and the hysterical fugue Every special kind of emotion to quote Professor Stout essentially involves a characteristic end or direction of activity mental or bodily anger tends to destroy or disable its object fear to avoid or evade it These substituted dramatizations of the hysteric likewise exhibit a tendency to accomplish the same end as would be served by the emotion those associated with fear or discomfort are obviously the most frequently observed but when brought to bay the patient may give a highly theatrical display of anger or resentment the fatuity of which is patent to the most superficial observer The symptoms which first served as a language for the expression of conflict assume in their own right an ever growing source of interest for the hysteric reinforced by the extraneous sympathy and minor sources of comfort which they may evoke They possess an additional attraction in that the concentration of attention directed to them makes it easier to ignore the memories of the unpleasant experiences in which they originated In an objective study of conduct there is little room for the theory of the dynamic value of the repressed complex on which so much stress is laid by many psychotherapists but the appeal to motor manifestations as adjuvants to the suppression of painful memories rests upon a sound basis of observation dating from the work of French neurologists on the pathogenesis of tics

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gravity or furnishing the patient with any hints that may be productive of new symptoms will satisfy himself as to the absence of any organic complication

The whole treatment consists in the establishment of what has been termed an atmosphere of cure It is confidently suggested to the patient that the symptoms can be removed and it is a question depending entirely upon the temperament of the physician and his estimate of the amount of cooperation he is likely to secure from the patient whether he relies on pure verbal suggestion or heightens its hold on the patient by reinforcement with some physical stimulus such as the application of a mild faradic current or manipulation of the affected part

In either case there is a golden rule to be observed— the first treatment must be personal never relegated to nurse or masseuse and once commenced it must never be relinquished till some objective success in the abatement or abolition of the symptoms can be demonstrated to the patient Once this is accomplished the atmosphere of cure is established and at the next session things go smoothly Failure to achieve some result acts directly on the patient as a suggestion that his symptoms are not removable by his doctor and on the next occasion success may be far more difficult to achieve or even impossible When considerations of time are likely to interfere it is far better to leave a patient untreated for several days rather than to commence a treatment which if not rapidly successful will have to be temporarily abandoned for other duties

The removal of the hysterical symptom or at least its abatement by counter suggestion should precede any attempt to readjust the attitude of the patient to the situation which precipitated the attack This precedence of treatment of the physical symptoms is a necessary corollary to what has been said in the foregoing account of the genesis of hysteria Inasmuch as the hysterical syndrome has been regarded as an abnormal reaction of an abnormal organism to a disagreeable situation it does not necessarily follow that the initial situation admits of any other qualification than that given to it by the patient In such a case failure to represent it in a more favorable light when it precedes the demonstration of the curability of the symptoms and the suggestion of self control may render these latter procedures extremely difficult Moreover whatever may have been the initial situation circumstances may have so altered that its memory is deprived of disagreeable associations but the patient has now acquired a facile method of reacting to all the minor conflicts of life—thus a soldier whose detestation of army life was expressed by hysterical manifestations may after demobilization still persevere in the same mode of expression as a reaction to all the petty annoyances of domestic life

system unbalanced by some abnormal stimulus but with an abnormal nervous system reacting abnormally to stimuli leading to states of conflict which occur equally in the experience of normal individuals Viewed from this angle the elucidation of the primary experience which led to the manifestation of the hysterical symptoms becomes a work of purely restricted therapeutic interest We wish by a superficial analysis to learn what this experience was in order to be able if possible to reassure the patient and to induce him to regard it from a brighter point of view and are not actuated by any belief in its specific character as a cause of hysteria It is therefore usually a matter of very superficial enquiry Only when the patient has sought relief in the assumption of amnesia are there any indications for an attempt to probe below the surface Here we are at once faced with the undoubted fact of the extreme suggestibility of the patient It is on this rock that so many psychoanalysts founder and the most casual study of the writings of the majority will convince an unprejudiced observer that the analyst finds what he suggests The psychology of suggestion is extremely subtle—an unconscious inflection of the voice a slight movement of the body emphasizing expectant attention will give the cue to a suggestible subject The story of the thinking horses of Eberfeld and the way that they detected the right number invariably owing to a slight assenting movement on the part of the innocent observer should give food for thought to those who undertake these infinitely more complicated investigations The purely objective nature of the word association method of Jung may indicate the nature of the disturbing complex in such cases as those in which the physician is at fault Reliance upon this method however occasionally leads to fallacious results It is by no means certain that the particular complex indicated represents that which is responsible for the appearance of the hysterical symptoms Several such complexes may be discovered in the life of any subject normal or hysterical nor can their acceptance by the suggestible patient count for much If however the observer wisely abjures pushing his analysis farther than the purely objective word association method and adopts that indication which most probably squares with what he knows of the patient s history his conclusions are more likely to be in accordance with facts than if he attempts any further refinement Holding the clue to the particular stimulus that has unchained the hysterical symptoms the procedure indicated is first to remove the symptoms and then to attempt to deprive the exciting cause of its efficiency

Treatment of Physical Symptoms

A brief and apparently superficial examination will precede any attempt at their removal The physician whilst avoiding any suggestion of their

the patient may be enabled to master his inability to react normally to conflict with the environment imposed by a disordered nervous system. The response to difficulty that manifested itself in the egocentric hysterical syndrome may with a wide outlook and a deeper sense of social responsibility be replaced by strenuous altruistic effort. This mode of escape is not possible for every patient nor is it altogether free from the risk of encountering circumstances that may precipitate a relapse. it is however a by no means rare experience to find a quondam hysteric as a religious or social worker successfully sublimating his neurosis and contributing work which if of not very high order is of definite utility.

The foregoing account of the pathogenesis and treatment of hysteria has been written as far as possible from the purely objective standpoint. Much has been omitted that is common currency in studies of hysteria from the subjective point of view. Much that is highly suggestive and illuminating may be gathered from the study of the writings of Jung and his school but the reader must never lose sight of the fact that whilst he may cautiously gain a deeper insight into the psychology of neurosis by subjective methods it is only when practising purely objective methods of observation that he can be relatively sure of his facts.

Treatment of the Psychical Condition

After a preliminarily successful treatment of the physical symptoms their primary psychical source is dealt with its probable effect on the patient's nerves is adumbrated and he is encouraged to regard it as far as possible as a thing of the past with which in his present state of restored health he could easily deal The more lightly but yet firmly this part of the process of countersuggestion is handled the more readily will it be accepted by the patient Complicated psychological explanations are to be avoided and whatever may be indications of sexual conflicts it is unjustifiable to do more than convey in general terms that they are common to the greater part of humanity Thus far treatment by countersuggestion given a physician possessed of patience understanding and a not too antipathetic personality would appear to be an easy matter nor does experience show that there is any great difficulty in dealing with the hysterical patient on these lines But when the physical manifestations are removed and the patient has been induced to take a rational view of his dilemma it is still idle to talk of a cure The abnormal type of reaction persists the patient still is the same self centered dependent suggestible complaining creature that he was before his physical manifestations drove him to the doctor A fresh conflict with his environment may again evoke the hysterical response Is there then no cure for hysteria? If our reasoning based on objective examination is sound there is none Nevertheless the prognosis is favorable Experience and the results of Kraepelin's investigation of the age incidence of hysteria alike suggest that towards middle life it tends to disappear It may be that the emotive reactions which depend upon the activity of the vegetative nervous system and its endocrine hormones again become normal It may be that the voluntary control of emotion and expression is reinforced At present we have not the data to theorize Till such a process of natural cure supervenes much may be done by rational management of the patient's life Where circumstances admit of it an avoidance of exposure to intolerable stress may tide him over the hysterical period of his life but more important is the cultivation of self control The hysteric abandons himself to his symptoms in an atmosphere of injudicious sympathy and indulgence he represses them when they sensibly aggravate the discomfort of his surroundings It is the unpleasant lot of the physician to convince anxious relatives of these verities Far more difficult is the arousing of the self respect of the patient—he must be taught to feel that such manifestations as he has indulged in are unworthy of him but unless this is done by a physician gifted with insight it will too often have the effect of converting the simple hysteric into an hysterical prig Lastly by a readjustment of ethical aims and values

CHAPTER XXXV

NEURASTHENIA

By T A ROSS

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Neurasthenia is a functional nervous disorder due to faulty psychological adaptation to the stresses of life Its symptoms are primarily somatic with the supervention of certain secondary mental symptoms and of some secondary organic somatic symptoms They may affect any region of the body and are in the distribution of the sympathetic system differing thus from hysterical somatic symptoms which are mainly in the distribution of the cerebrospinal nerves They differ further from hysterical symptoms in that they are those of overaction whereas the former are mainly those of a negative response They represent an ineffectual but constant struggle against a difficult environment

Symptomatology

The most prominent symptoms are as follows they are never single but need not be all present

General—Fatigue on slight exertion is always complained of It will be discussed more fully later on Loss of weight is usual and is due partly to loss of appetite partly to interference with digestion

Alimentary System—Anorexia capricious appetite dryness of the the mouth dyspepsia are common symptoms The dyspeptic symptom usually complained of is fullness after food along with this there is often some dilatation of the stomach and retarded motility Definite and persistent complaint of pain after food is not usual and should put the practitioner on his guard especially if the pain has regular time interval The dyspepsia is frequently selective in a way that is incompatible with reality thus the patient may be able to digest beef but not mutton fried fish but not boiled fish and so on Vomiting is not very common when it occurs in a

rest very often when he is sitting quietly in a chair doing nothing as he will express it but when it will be found on investigation that he was brooding over something

Vasomotor System —Blushing sweating coldness of skin are vasomotor symptoms The sweatings may be extremely profuse and drench the patient He usually says that they are very weakening Seeing that sweat is merely a dilute urine and that many people take frequent Turkish baths without any feeling of being weakened it is doubtful if sweating per se is an exhausting thing though there is no reason to doubt the patient s veracity when he complains of feeling exhausted after them There is no analogy in reality though there may be in the patient s mind between sweating in this condition and sweating in a wasting disease like phthisis There the weakness is dependent on grave intoxication with disease products and not on the sweatings though they accompany it Coldness of the skin is common and may lead to an absurd fear of catching chill so that the patient will wrap himself up in a ridiculous way in hot weather

Respiratory System —Dyspnea on slight exertion is common This system is on the whole free from neurasthenic symptoms Cough is found in hysteria

Nervous System —(1) *Somatic* —Peculiar feelings in the head occur often These are often described at first as headaches but closer questioning reveals that they seldom amount to pain the definite complaint of which should again put the practitioner on his guard They are rather feelings of discomfort of a band being tied round the head bursting feelings stuffy feeling weight on the vertex pressure on the frontal and occipital regions They are usually constantly present with exacerbations which last for hours and days and which will be found to be associated with anxiety

Of ocular symptoms there are two of importance muscae volitantes and functional asthenopia Muscae volitantes are present in all eyes and can be seen by anyone who takes the trouble to look for them Commonly we ignore them just as we can sit working in a room where there is a ticking clock and not hear it until our attention is drawn to it when for a time it is difficult to avoid hearing it The neurasthenic having one day seen his own muscae fixes his attention on the phenomenon because he fears that they mean either ocular disease or liver trouble An explanation like the above will abolish them from consciousness

In functional asthenopia the patient can see to read quite well for five or ten minutes and then the letters become blurred and often run together so that he is obliged to give up Pain in the eyes and headache are frequently associated with the attempt to read The eyes should be examined for errors of refraction and any error over 0 5 of astigmatism or hypermetropia should be corrected but despite what has been written by many

functional nervous disorder the patient is probably of the hysterical type This dyspepsia depends on a real alteration of gastric secretion and delayed motility although there is no structural disease of the stomach It has been shown experimentally that emotional disturbance alters the gastric secretions and therefore the discomforts of which the patient complains are genuine though they depend on a mental condition Constipation is common There may be mucous colitis The utmost care in excluding organic disease is necessary when this symptom is present

Urinary System —There may be pains in connection with loose kidney There is little doubt that much of the pain connected with this is functional in origin It is quite common for patients to develop pain only after they have been informed that such a condition is present It is then usually of a dull aching character Physical treatment relieves it if it is believed in by the doctor and patient It is on this account that surgeons differ so much in their views on operations for its relief The reasons for this will be seen after perusal of the section on treatment Frequency of urination is common especially after agitation of any kind On such occasions too it often occurs that the urine is large in quantity This may become a prolonged affair and be associated with thirst and the fear of diabetes It is probable that these cases constitute the condition called diabetes insipidus

Genital System —Impotence may occur in the male and is always a source of great distress The patient is apt to consider that it has been caused by previous excess or self abuse and to think that it betokens a grave condition of mental and bodily ill health

In the female dysmenorrhea may be a purely functional condition The diagnosis here is difficult and will probably be made with certainty after the patient has been successfully treated for other neurasthenic symptoms Dyspareunia and vaginismus in the absence of local organic disease are probably always neurasthenic in origin They usually arise because of some fear of or disgust towards the sexual act

Circulatory System —Tachycardia cardiac discomfort often amounting to pain palpitation sense of constriction in the chest with fear of death are symptoms frequently encountered When these symptoms occur in young persons who are free from organic diseases affecting the circulatory organs such as valvular disease pulmonary or kidney disease anemia one of the fevers etc they betoken a neurasthenic condition Many cases of soldier s heart belong to this group The presence or absence of the effort syndrome is a useful diagnostic point If a patient is asked to run up about twenty steps his pulse rate will quicken If it returns to the normal within a minute and a half the absence of organic impairment of the muscle may be assumed In all these functional circulatory disturbances while exercise may bring on the symptoms they occur also while the patient is at

awkward in company or awkward among traffic and so he develops a secondary fear of these which may be quite simple in origin and much easier to treat than the phobias which are primary to neurasthenic symptoms and which are dealt with under the article on psychasthenia

Fatigue is often described as the most characteristic symptom of neurasthenia and many forms of treatment have been devised which have its cure as their basis Fatigue is however a complex idea and stands for different sets of things If we work our muscles to an excessive amount fatigue sets in which after a longer or shorter period becomes imperative so that we must lie down and rest Even after any great fatigue the sort that was achieved in the retreat from Mons recovery follows in a few days This physical fatigue may conceivably be toxic or it may be due to an exhaustion of energy like the exhaustion that overtakes an electric cell when its energy has become run down Both toxic products of muscular work and exhaustion of nerve energy are soon removed by rest but the fatigue of which the neurasthenic complains does not resemble this It continues for months and years Prolonged periods of rest may fail to influence it in the slightest degree as soon as the patient gets about again he may feel utterly tired Although he may say that he is fatigued after the slightest effort careful enquiry will often show that this is only partly true Certain activities will often be unimpaired and it will be found that those which can be made easily are for the most part those which give pleasure and that those which cause fatigue most readily are the things he does not wish to do Thus a certain patient described how utterly exhausted she was if she had to wash the head of a little girl who lived under her care She cited that as an example of what ought to cause fatigue to no one Subsequently in the course of her treatment it transpired that she could bicycle fifteen or twenty miles without any fatigue at all This sort of fatigue rather resembles that which we all feel after a day on which we have been very worried and anxious but during which our muscular output may have been inconsiderable It resembles the fatigue of a regiment marching on a dusty road which is dissipated by the order that the band shall strike up

The question then arises Is fatigue of this kind only a sensation or does it correspond to any objective reality? The answer to this is not simple Probably it is partly only a sensation But it is certain also that worry anxiety and doing what we strongly dislike doing (for to do that is to be worried) use up bodily energy in an extravagant way We know from the researches of Cannon and others that the emotions cause an increase of adrenalin secretion with the liberation of excess of sugar into the blood These are signs that energy is being expended somehow though there may be no visible work to show There is therefore real fatigue The patient has been struggling against his difficulties and there has been overaction

ophthalmologists errors below this do not need correction and the patients are better without it There is an idea that patients with small errors are making constant effort to see clearly and so tire out the ciliary muscle This is quite unfounded Astigmatism up to 0 5 occurs in the large majority of people and what is normal is not a cause of disease Secondly when the case is investigated in the manner discussed later it will be discovered that the difficulty began when the patient was reading something that upset him and that its occurrence led to fears that if he continued to read it would damage his eyes in some serious way When the patient realizes that this will not happen the symptom will disappear It may be regarded therefore as a biological defence against fear the fear of blindness just a flight from the attack of a wild animal is a defence against fear of injury When the patient realizes that there is nothing to fear the necessity of the defence has gone and the symptom disappears The condition is one of great importance It cuts the patient off from the most valuable means that any of us possess of escaping from the dreariness of life It is very common

Giddiness is frequently complained of It is a subjective sensation of being giddy not an apparent objective rotation of external objects It is frequently associated with asthenopia when the attempt to read is made

Algias and discomforts are present in various parts of the body The commonest are a feeling of a claw in the abdomen rectal pain persistent peculiar feeling in the epigastrium the pain of loose kidney pains in the limbs often described as rheumatic

Insomnia is one of the most important nervous symptoms and to some degree is almost always present It may be of several types difficulty in getting to sleep broken sleep wakening early and finally at three or four in the morning It is seldom that there is no sleep The patient wakens unrefreshed and is more tired than when he went to bed He complains frequently of distressing dreams The patient always attaches great importance to his lack of sleep the discussion of this and of the significance of some other symptoms will be found in the section on treatment

(2) *Mental* —Inability to concentrate or to remember the latter obviously follows the former if we have not concentrated on a subject we cannot expect to remember much of it The inability to concentrate is natural seeing that the patient has all these other symptoms continually being forced into consciousness so that he cannot attend to anything From these two symptoms and from the insomnia springs one of the most important symptoms of all *viz* fear of insanity Nearly every neurasthenic is haunted by this fear He feels confused and unable to use his brain and considers this to be a sign that his mind will give way

Because of the inability to concentrate the patient may find himself

asthenopia may be perpetuated They are begun by some external anxiety the relation between this and the onset of the symptoms is overlooked the symptoms themselves are regarded as indicative of serious disease and the anxiety about this keeps them in being Apart from the fact that the whole training of large masses of the laity leads them to look for causes of illness in the weather the atmosphere food dampness draughts and the like there are good personal reasons why a patient should not think that his own thoughts can cause illness It is humiliating There is a feeling that if such a view is true the illness has been cowardly or foolish there is a feeling that the doctor must think that the patient is putting it on and no one will admit without difficulty such a possibility for himself though he can do so easily for his neighbors There is yet another reason why he should not see that a psychical cause may exist for his symptoms the exciting cause may have been forgotten While one significance of this is that it tends to obscure from the patient s vision the fact that his illness is mental in origin there is another aspect of it which is of the utmost importance *An idea does not need to be necessarily in full consciousness to be effective* Normally we see this every day We do not collide with our fellow passengers in the street though their presence and actions may be hardly in consciousness we are thinking of something else It is a common enough thing that our first consciousness of something we have observed occurs in a dream Thus a patient was accustomed to walk along a certain hedge in which he was certain he had observed nothing special One night he dreamt that he saw in that hedge a nest with eggs He went there in the morning and found them as he had dreamt There are two possible views about such a dream one that he had a revelation of the presence of the nest and eggs vouchsafed him in sleep the other that some part of his mind not conscious had observed them that the tendency of this to come into consciousness had been for some reason frustrated probably because his conscious mind was occupied by something more pressing but that that tendency had been gratified when the ordinary working mind which chooses some subjects for thought and rejects others was in abeyance during sleep If this be granted it is not a far step to predicate that the conscious waking mind has a power of selecting what it shall think about but that if it rejects a subject that is not to say that the subject rejected is not in the mind at all It may come into consciousness when it gets the chance

Now it seems to be a fact that the mind does tend to reject experiences which are of an unpleasant character It attempts to do so in various ways One is by the substitution of a word which in itself does not convey the full meaning Thus a plain word like asylum tends to become refined into mental hospital keeper becomes attendant belly becomes stomach and so on This device is used when the subject to be talked of is one that must be

both of mind and body His fatigue is not simply a sensation nor simply a real fatigue but a combination of both

The above list of symptoms is not complete but it comprises the most important and most common When we consider it carefully it will be seen that these are the symptoms which are often associated in ordinary life with the presence of anxiety When we are worried and anxious we feel tired have uncomfortable heads cannot concentrate sleep and eat badly and our digestions are apt to be upset A history of anxiety will be found to be closely related to the onset of symptoms and relief from that anxiety will remove the symptoms

To make this clearer let us consider the genesis of an actual case A man has financial worry and thinks he will be ruined He returns home and says nothing about it finds he has little appetite but in order to avoid attention eats his dinner Because he is anxious the buccal gastric and other digestive secretions are scanty and he therefore probably gets indigestion after the meal At night he lies awake seeking a way out of his difficulties ultimately falls off into a sleep broken with bad dreams and wakens unrefreshed with a thick heavy sensation in his head and the feeling that he is not as fit as he was yesterday to attack his difficulties One of several events may happen The external anxiety may clear up but the man may now have created a set of secondary anxieties about his health Thus he may have thought that his dyspepsia betokened some condition of the stomach which called for careful dieting he may put himself on a rigid diet and for a time the dyspepsia may improve But he has now surrounded himself by a wall of restrictions out of which he would like to escape but fears to make the attempt to do so Some day he may break his rule but he does it in fear of the result and this very fear which is a form of anxiety may be enough to give him a dyspeptic attack Or he may have some other external anxiety while he is rigidly following his dietetic rules and he has another attack of dyspepsia which disturbs him because it came on while he was careful of his diet He therefore makes more rules but now always eats in fear of the result and so never has a comfortable digestion

Similarly with sleep at the beginning of his anxiety he has a poor night he ultimately drops off into unrefreshing slumber with disturbing dreams and next morning awakes more tired than when he went to bed If the external anxiety continues the same kind of night is repeated After a little the anxiety may have been relieved but now he goes to bed fearing the ill results of sleep itself that he will be totally unable to do his work if he does not sleep that he will in some way damage his brain that he may lose his reason Any of these anxieties may give him a bad night and they may repeat themselves indefinitely and so the insomnia may continue indefinitely

In exactly the same way palpitations sweating polyuria headache or

Addison's disease, phthisis or pernicious anemia, true dyspepsias like gastric ulcer and cancer, real nose diseases and refractions of magnitude cause no collection of symptoms in the least resembling those described and therefore it is unlikely that such causes can have anything to do with the pathogeny of neurasthenia. If it is urged that treatment for such conditions has *cured neurasthenia, it suffices to say that as the disease is due to anxiety* so it is benefited by hope and therefore any treatment by an enthusiast will temporarily at least help these patients.

DIAGNOSIS

Diagnosis must be made from organic disease, from other functional nervous disorders and from the psychoses. In diagnosis from organic disease there is a twofold difficulty. Many organic diseases have a neurasthenic element added to the organic state. Some of the symptoms therefore in every condition of illness are neurasthenic. A man who is ill with influenza worries about the fact that he is away from business, he feels weak after the fever has gone and becomes anxious as to when he will be able to return to work, and so on. These anxieties will produce some symptoms and if these in turn are looked at in too serious a way the seeds of a post influenzal neurasthenia have been sown. So with heart disease, kidney disease, especially where the doctor attaches undue importance to the presence of physical signs. Perhaps no modern instrument has been more responsible for a secondary neurasthenia of this kind than the sphygmomanometer. The *accurate measurement of blood pressure being new* has not yet fallen into its proper position and there can be no doubt that the significance of rise of pressure has been on the whole overestimated, a thing liable to happen with each new discovery. Fear arising partly from the doctor's gloomy views and partly from the want of real knowledge about the significance of the phenomenon is implanted in the patient's mind with disastrous results.

The second difficulty arises from the fact that although no organic disease is present the doctor is afraid that he may be in the presence of some obscure disease such as early phthisis. It has become the fashion to insist that if successful treatment of this disease is to be hoped for, the diagnosis must be made before physical signs arise. Grave responsibility from the nervous point of view rests on the doctor who does so. If the state of ill health has lasted for some months and there are still no signs on careful examination by modern methods, it is extremely unlikely that organic disease is present. It is not common for the neurasthenic to come to the doctor at all till his symptoms have existed for some months. In practice

thrilled of sometimes When there is no such necessity the idea often tend to be excluded from consciousness altogether But though we may desire to exclude a subject it is found that certain things with which it is associated tend to bring it into consciousness Thus the present writer used to feel depressed at the smell of lily of the valley On going into the matter he found that lily of the valley was associated in his mind with dead bodies friends often lay these flowers on the body As a young doctor he was absurdly sensitive about each of his patients who died thinking it was his fault that some one else might have done better What was happening then was that lily of the valley was stimulating memories of failure to come into consciousness He was resisting this technically he was repressing and therefore there was conflict in his mind productive of a sense of discomfort Now awkwardness and shyness in company fear of the street in the dark and similar symptoms are frequently due to the fact that company noise (sometimes any noise sometimes special sounds only) are things which stimulate the recall of certain memories which the patient is endeavoring to suppress conflict ensues and that conflict produces symptoms which may be of any kind Thus a certain man who was waiting to see the doctor was suddenly seized with palpitation He had dreaded heart disease and had often been assured that he had none This attack came on while he was sitting quietly and the only thing he could say was that he had heard some one speak in a harsh voice On going into the matter with him he himself stated that the voice made him think of the words come back soon" though that was not actually what he heard them say Longer thought brought out the statement that the voice resembled that of the manager of the bank where he was a clerk and that these words had actually been used to him by the manager some days before when he said he wished to have time to go to see a doctor at a hospital The tone which had then been used had made him see that the time was grudged and he had feared dismissal He had endeavored to banish the idea from his mind but it i easier to banish an idea from consciousness than from the mind As Morton Prince says the patient tries to put it out of his mind he is really putting it into his mind Therefore a voice resembling the manager s tended to bring the idea of the latter into consciousness He repressed that There was conflict which caused palpitation For further information on this aspect the article on psychasthenia should be consulted

Many other views on the etiology of neurasthenia have been put forward It has been regarded as a real exhaustion of nerve force as a toxic condition from the intestine or from what has been called subinfection as due to dyspepsia to nasal disease especially nasal spurs and septal deformitie to errors of refraction to uterine displacements and to other organic causes It may be pointed out that true infections true exhausting diseases like

a depressed type of general paralytic who at an early stage may be mistaken for a neurasthenic before the onset of physical signs The diagnosis at this stage is not very important as the paretic patient is not likely to do any harm before he shows disorders of conduct which are easily recognized

Treatment

The first stage in successful treatment is a careful and painstaking examination The object of this is not only to make a diagnosis but also to gain the confidence of the patient To accomplish this it is essential that the doctor should listen once at least to all that the patient has to tell him and it is advisable that notes should be taken of what is said When the patient has finished he should be asked about those regions and systems of the body which he has omitted to mention Care must be taken to enquire about mental functions also especially about depression the condition of the memory power of concentration fears and anxieties This is a procedure which is often left out of set purpose It is stated that if a nervous patient is asked if he has a cough he will acquire one in a few days and that the doctor has suggested the symptom Certainly if the question were asked in an anxious tone and if it were an isolated one such an unfortunate event might follow but if it comes merely as one in a series and it is clear that the doctor is only making a routine enquiry about all the bodily and mental functions the patient will not be led to think that there is the suspicion of any special disease and no harm will follow If the plan is not carried out awkward things are apt to happen later on It is disconcerting to find after weeks of treatment that a patient whose complaint was insomnia was really suffering from fear of impotence It will be no offence to enquire why the patient did not mention this he was shy and did not like to or he thought that the doctor would have enquired about his fears had he thought them important

The tale of symptoms being complete the attempt should be made to fix the time of their onset though at the first interview nothing very definite may be obtained The symptoms are never single and they have had a gradual growth symptom has been added to symptom as the case progressed The first manifestations will have been slight and may be forgotten and therefore though the patient may give a date it will be found subsequently to be incorrect

Questions should be asked about other illnesses and the attempt should be made to ascertain something of the general attitude of the patient towards life both now and formerly What are and what were his interests did he lead a normal life in childhood and adolescence did he play games etc ?

therefore this difficulty in diagnosis should not arise In more advanced organic cases the question is one of physical examination made with ordinary care

From hysteria the diagnosis is made by observation of the physical signs which in the latter attack the cerebrospinal distribution rather than the sympathetic by the fact that the hysterical patient is not much disturbed mentally by his disability his placidity about it being in strong contrast to the neurasthenic's anxiety by the fact that the hysterical symptom always implies a loss of function a loss of sensation a paralysis an amnesia whereas the neurasthenic's symptoms are those of overaction

From psychasthenia the condition is distinguished by the prominence of mental symptoms in the former along with the absence of bodily symptoms by the fact that reassurance has no effect on the psychasthenic whereas it has great effect in the neurasthenic

It must be admitted however that the line between neurasthenia and psychasthenia is not a clear one Many neurasthenics will get rid of their physical symptoms and retain their mental ones many psychasthenics superadd somatic symptoms to their mental condition Neither in a wide sense is there a clear line between the neurasthenic and the hysteric If under great stress the neurasthenic gives up the fight and retires from it he may develop hysterical symptoms and conversely, if these are cured by suggestions directed to the symptom alone neurasthenic symptoms may appear This was specially notable during the war when if a man was cured of hysterical paralysis he was liable to acquire insomnia headache sweatings etc These might be looked on as indicating that he was once more trying to face the ordeal of returning to the war

In hypochondria there is a fixed idea of ill health which is irremovable It may be possible to show the patient that his trouble does not depend on what he holds it does whereupon he immediately changes to some other region He may be convinced that his liver is normal and then decides it is his kidneys that are out of order Strong persuasion convinces him that they are healthy when he fixes on his heart and so on

The diagnosis in the early stages of dementia praecox may be very difficult and it is only when some very marked disorder of conduct occurs that it can be made

The depression of the depressed stage of manic depressive insanity is more profound in that it is not amenable to persuasion of any kind The symptoms are much more steadily present Delusions are common The diagnosis is very important because of the risk of suicide Neurasthenics never commit suicide and it is harmful to watch them Any depressive may do so

General paralysis as a rule does not cause difficulty There is however

As was shown in the paragraph on fatigue the patient is one who is exhausted in mind and body after a struggle against the difficulties of his environment Two things are therefore needed he must be rested and built up he must be taught how to manage his life with less struggle

It need not be laid down that every case requires rest in bed but all those which are advanced do At the beginning this had best be absolute except that the patient may rise to have a bath and to move the bowels and empty the bladder The period of this rest should seldom exceed three or four weeks

Mental as well as physical rest must be secured No rule of thumb can be laid down for this Some people can rest quite well in their own homes others will accomplish their end better in a nursing home away from all contact with friends and from correspondence There are those whom such a plan would depress though it is also true that many think that they will not rest under these circumstances who enjoy it when they have tried it Many women say that they could not rest away from their homes and children though these may be the very things which are keeping their illness in being As regards correspondence a large amount is incompatible with rest even a weekly home letter may be disturbing Some patients on the other hand will fail to get mental rest unless they receive a short line from home every day

The doctor himself must be the judge of what is to be done and once his decision is made and accepted he must adhere to it He will be well advised if he is a beginner at this kind of work to insist on complete change from home and no letters at the outset of the treatment he will himself keep in regular communication with the patient s home and give a faithful report of the health of its inmates As he grows more experienced he will learn where he may safely relax the rules The duration of the mental rest will roughly coincide with the physical In both the return to activity should be gradual

Reading may be allowed from the outset The daily paper may usually be permitted books at the beginning should be unemotional and not requiring much concentration

It was stated that these patients usually have anorexia and dyspepsia and that they have become thin Along with this a dilated atonic stomach is common The horizontal position allows an atonic stomach to perform its motor functions more easily and improved appetite and better digestion follow Because the stomach is in an atonic condition the diet must at *first be small in amount and simple in character and full diet be achieved* only gradually

From the outset psychotherapy is being practised The method of case taking already described in addition to its being essential for diagnosis is

All this takes time but time is essential it is not necessary that it should be accomplished at one sitting though it is better that it should be It does not take longer than the performance of even a minor surgical operation and most doctors find time for that Next the patient must be examined physically and this should be very thorough not only for the purpose of excluding organic disease but also that the patient may receive sufficient assurance on this point It should be remembered that many of these patients are old hands at being examined and that a doctor who makes a slovenly examination will be detected by them and will not be believed when he tries to assure the patient that there is nothing wrong with the organs of the body This examination should be made once for all repeated examinations will convey to the patient s mind the idea that the doctor is not sure What the patient is told is important If the doctor is sure that there is no organic basis for the symptoms the patient should be told so If further evidence is required such as is yielded by the sputum or cerebrospinal fluid or by consultation with a specialist the opinion is withheld till this is done If the doctor is not sure even after this he should say so No loss of confidence follows this The patient is pleased with honesty and will be willing to wait till the case has been watched for a longer time

If there is no organic basis the patient is told that his symptoms depend on a mental attitude and an explanation of how the mind affects the body is given It is shown that in everyday life mental events cause physical symptoms that anxiety causes headache insomnia anorexia that fear is followed by tremor or dumbness ("struck dumb with terror") that disgust produces vomiting etc The patient may say that he has none of these mental feelings but if the history has been taken carefully it will be easy to show that his symptoms did begin or get worse at time of strain and anxiety

If organic disease is discovered the patient should be told what it is he probably knows already If it has any relation to the symptoms complained of this should be admitted if it has none the reasons for such a view must be given with lucidity In this matter of explanation two errors are often made on the one hand organic disease present is scouted if the patient knows of its presence this will be followed by instant and complete loss of confidence on the other hand some abnormality which has no relation to the illness is given as its cause Great harm ultimately results from attributing widespread or remote symptoms to nasal spurs and the like Harm too is done by want of clearness Opinions such as 'weak heart but not diseased' weak lungs are great creators and preservers of neurasthenia They are expressions which are devoid of meaning to the doctor himself and therefore to the patient they convey only doubt and anxiety and so increase the disease which has its origin in doubt and anxiety

foods of a household are digestible if only he will believe it It is not wise to introduce any of the special adverti ed foods if success follows it is a misfortune for the future the patient will believe that it was the special food and not his altered state of mind that caused the improvement and his dependence on himself will be assured by so much the less

Insomnia also must be attacked early the condition is provocative of alarm Most consider that if it continues they will lose their reason or damage their brains in some irretrievable way The patient should be told that these fears are groundless that bad sleep is depressing but not dangerous It may be pointed out that interest of any kind tends to keep people awake Brain workers with a large output sit up late and the interest of their work keeps them awake till one two or three in the morning They do not call this insomnia and they do not feel ill because of it rather they congratulate themselves that they can do with so little sleep so with pleasure seekers who will stay up dancing night after night and certainly not feel that they are losing their reason the interest of their pleasure keeps them awake and it is only when this pleasure begins to pall that they begin to feel tired Now worry and anxieties are kinds of interest they are not of a desirable kind but they are interests in oneself instead of in omething objective When they keep people awake the condition is now called insomnia and all orts of evil results are feared But the actual lying awake can be no more harmful in the one set of cases than in the other and the reason why the one set feel ill next day and the other not is not because of the want of sleep but because of the accompanying anxieties which the patient has already learnt are the cause of his symptoms It will be found that the commonest anxiety is about the effect of want of sleep itself and if some explanation like the above is given three fourths of the patients will immediately begin to sleep well No promise however that this will happen should be given the patient should be promised that he will be able to lie quietly in his bed and not feel so ill after a poor night Those to whom such an explanation does not bring sleep will be found to be suffering from some other anxiety to be dealt with in the manner shown below It is not usually necessary to give hypnotic drugs and if the physician is forced to do so he should feel that he has so far failed with his case If they should be given a dose of seven grains (0 45 gm) of ome drug like veronal or medinal should be administered in a cachet The dose hould be gradually reduced by a grain a night and a grain of ome inert substance added so that the patient cannot see the difference No deception is to be practised the patient is told that this will be done but that he will not know what night the alteration is made When he has slept three or four nights without drugs he should be informed of the fact when he will be ready to go on without e ern l help

a psychotherapeutic measure of importance day by day other measures are employed At first it is best that these should have reference to the symptoms only and among the first symptoms which will need attention are the digestive The patient may say that he cannot be expected to eat if he is kept in bed He is shown how bed favors the action of a feeble stomach he is informed that people with fractures who are necessarily *confined to bed are as a rule able to eat just as much as when they were up* and about He will give a list of foods which he cannot possibly touch and here his ideas may be successfully attacked from two sides First he can be shown that the lists of foods which he can take and cannot take have no real relation to their digestibility In his forbidden list will be found things more easily digested than in his approved list Secondly from his history it will be seen that his dyspepsia began and got worse at periods of mental stress He should be told that it is known that anxiety alters the gastric secretion and delays the motor action and that there was therefore a real dyspepsia due neither to the food he had eaten nor to the state of the stomach but to his mental state alone He will probably then be easily led to see that he made the error of ascribing his symptoms to a particular class of food and that if he had to eat that kind he did so in a condition of anxiety and that this secondary anxiety was then the cause of further dyspepsia When this had gone on long enough there were almost no foods that he could eat without anxiety, and therefore his dyspepsia became fixed This was then followed by chronic lowering of stomach tone physical weakness was superadded He must now be led back along this road *He is shown that the atonic stomach works best in bed This* gives confidence and he will therefore eat in hope and not in despair He is promised that the food will be carefully regulated that at first only small amounts will be given and this of a simple nature that day by day this will be added to in accordance with a well tried plan All this regularity and method replacing his own chaotic gropings will inspire confidence and with that the battle is won The following plan is not to be regarded as a rigid scheme but as an indication The details must be worked out for each individual If milk is available it is convenient to start with about half a pint and a small slice of bread and butter every three hours the first day every two hours the second a larger piece of bread and butter is added the third an egg the fourth a milk pudding at midday the fifth then fish fowl meat in succession till at the end of ten days the patient is taking the ordinary full meals with 2½ to 3 pints of milk some of which is taken with the meals and some halfway between them The patient should be brought up to about his normal weight there is no object gained by making him fat Though milk is of great assistance it is not essential any ordinary diet will do provided the patient is induced to see that all the ordinary

part of this method is that he should not deliberately try to think of a cause but only try to remember a period with its environment when the desired memory will often slip in. Thus a certain patient was always uncomfortable in company so that he was never able to enjoy ordinary social intercourse. He also dreaded some serious disease of his kidneys and no amount of reassurance by many doctors had been able to undermine this. It was found that the latter fear was connected with the fact that he had some what puffy eyelids; he had learned from one doctor that that sometimes indicated renal disease. But he had invariably been unable to get comfort from the findings in the urine. By going further back it was discovered that at the age of fifteen he had been told by some companion that his eyes showed that he practised masturbation. It was true that he did so and he was therefore prepared to believe that the facial sign was indeed pathognomonic; as he did not see many eyes like his own he naturally concluded that he was doing this certainly in excess of what other boys did. As he did not know how common the knowledge of this sign was he naturally became shy in company and this persisted. He thought his debased character was stamped on his face. He had, however, struggled to keep about and the constant effort and anxiety had exhausted him. It was easy to show him that the sign was false and to get him to believe that all people are subject to sexual thought and that most boys masturbate. He then became well. It may be noted that the fear of kidney trouble was a more tolerable thought than the other and therefore was not easily parted with.

By pushing the conversation back over the years many difficulties will be brought to the surface and in almost all the doctor will be able to make the patient see that there is a better way of looking at them than that hitherto practised. These people are overscrupulous and have been calling themselves cowardly, vicious, untruthful, greedy and selfish when they have only been thinking what we all sometimes think and practising what we all sometimes practise. It will not be difficult to show them that we all have thoughts of which we are ashamed and that often we have yielded to them, but that surprisingly often we and they have overcome them and that when we have overcome them we may be proud; for shameful thoughts are temptations and there can be no virtue but only innocence, a pretty but a valueless thing, in the absence of temptation. The doctor need not fear that he will be held guilty of cant if he speaks like this; he will get no opportunity to do so till he is far into the patient's confidence and it will then be the natural and obvious thing to do. When this has been done the primary symptoms will disappear and the patient will have acquired such insight into his condition that relapse need not be contemplated.

The causal ideas may be fully in consciousness outside the focus of

The fear of insanity depends not only on poor sleep but on the mental disabilities the lack of concentration the acts of forgetfulness the various fears which beset these patients As he is engaged in continuous struggle it is small wonder that he cannot concentrate on anything besides this struggle as he does not concentrate on his daily affairs he is forgetful as he is in constant dread of the future he has fears They all depend on the presence of some anterior symptom and when he has learned how to deal with this they will disappear in the meantime he can be assured that this is not the way people lose their reason There are certain specific fears such as those of the street of closed rooms of people of trains which are discussed in the article on psychasthenia

About the other general symptoms similar assurances must be made It must be shown that palpitation will occur in a healthy heart on emotion that after this has occurred several times nervous people will begin to be anxious about their hearts and dread heart disease and that this fear is sufficient to keep the palpitation in being So with polyuria headache and the other symptoms

The psychotherapy so far has dealt only with the persistence of symptoms and not with their origin and lasting cure demands that this should be laid bare Unless this is done it will be found that certain symptoms do not disappear The reasons why this happens are somewhat complicated It may be that the patient has not associated certain causes with certain effects it may be that he has actually forgotten the causes which are then said to be repressed into the unconscious Though these repressed causes are never in consciousness they may still be active and provocative of symptoms It is beyond the scope of this article to enter into a prolonged discussion of the nature of the unconscious which is dealt with in the article on psychasthenia It must suffice here to describe a simple method by which the physician can bring to light the causes of distress which have not come out by the simple taking of the history As the mass of symptoms is reduced by the treatment above described some will be found to remain and these must now be carefully investigated The patient who will now have considerable confidence in the doctor will cooperate more readily than he would have at an earlier stage He must be asked to think back year by year month by month till he comes to a period when the symptom was not present and had never been present At first he will say perhaps that no one could go back far and be sure but if he is encouraged he will often arrive at a conclusion with confidence This enquiry may take him back twenty or thirty years He is then invited to make a mental picture of his environment about that time the house he lived in the people surrounding him and so forth Very often there will flash into his mind something which will throw light on the onset of the symptom The important

CHAPTER XXXVI

PSYCHASTHENIA

By BERNARD HART

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Introduction

The term psychasthenia was originally introduced by Janet to designate a group of the neuroses characterized by the presence of obsessions phobias states of anxiety hesitation and doubt and various other symptoms The nature relationship and position of the disturbances thus collected by Janet into a single clinical entity have been for long and for that matter still are the subject of considerable dispute and divergence of opinion Under these circumstances a clear understanding of our present knowledge with regard to the disorders in question can best be achieved by approaching them from an historical standpoint and we shall therefore commence by passing under review the various conceptions which have been employed in their explanation and classification during the past hundred years

attention but brought there fairly easily or they may have been pushed wholly out of consciousness and be incapable of recall by ordinary thinking Even in the last case careful thinking back may bring them to the surface If they cannot be brought back the Freudian technique may be employed but it is a dangerous weapon and in any case cannot be described here If the patient is beyond the methods described he is more a case for a special ist

As soon as it can be managed the patient should be engaged in some regular occupation This may be started while he is still in bed and cer tainly should be part of his daily life as soon as he begins to get up He has lost confidence in the power of accomplishing anything and he will regain this nowhere so easily as under the superintendence of the doctor whom he has learned to trust If he has any special aptitude that should be encour aged if he can draw or paint let him do these If he has no aptitude let him be encouraged to try something In an institution it is easy to provide a variety of work such as carpentry book binding weaving etc In private a little ingenuity will discover something The work should be useful when possible so that the patient may feel once again that he is doing something to help on the work of the world He must expect that at first it will be difficult and discouraging this we all feel at times even when we are well and therefore he must not look on it as something which is a sign that he is not yet fit to begin He must persevere even on those days on which he feels it very hard

Finally it may be pointed out that the development of a neurasthenic attack is largely in the doctor s hands The doctor who listens carefully and alone to his patient s story for they will not tell all in public who is careful in his physical examinations who does not fear to say exactly what he finds and who possesses judgment so that he is not led away by every fantastic whim of medical fashion will have few neurasthenics in his practice He cannot escape them altogether but their cases will not grow into the helpless and hopeless beings that are the bane of everyone s exis tence who comes into contact with them

Compulsive Phenomena	1 Compulsive Ideas (Obsessions)		Obsessive ideas and obsessive impulses
	2 Compulsive processes (*agitations forcées*)	a Intellectual	Systematic—Mania Diffuse—Rumination
		b Motor	Systematic—Certain tics Diffuse—Crises of agitation
		c Emotional	Systematic—Phobias Diffuse—Anxiety (*angoisse*)
Stigmata	3 Subjective feelings of deficiency (*Sentiments d'incomplétude*)		Subjective feelings of inadequacy in thought action and emotion Feelings of unreality and of depersonalization etc
	4 Actual psychological deficiencies (*Insuffisances psychologiques*)		States of hesitation and doubt wandering attention revery in place of directed thinking etc
	5 Physiological disturbances (*Insuffisances physiologiques*)		Headaches digestive vasomotor secretory disturbances etc

The e various symptoms which practically include all the disturbances forming the subject of the present article will now be defined and described and we shall then pass on to consider their relationship and the principles underlying Janet's method of grouping them

Compulsive ideas and processes comprise a number of mental phenomena whose characteristic feature is the intrusion into the patient's mind of some idea or process which has no adequate foundation or relevance but whose entry and development are accompanied by a feeling of irresistible compulsion The term obsession is sometimes applied to the whole group but is more often limited to the subdivision of compulsive ideas

Compulsive Ideas (Obsessions)

Obsessive ideas are ideas which force themselves into the patient's consciousness apparently against his will and upon which he feels himself compelled to dwell however distasteful or repugnant they may be to him Thus a devoutly religious girl may be tortured by an obsession consisting in the conjunction of the ideas of God and of some obscene object Whenever she thinks of the Deity then immediately there arises in her mind the thought of penis fæces or water closet Another patient is obsessed with the thought that she is becoming fat and spends anxious hours examining her body to determine whether or not the dreaded signs of obesity are becoming apparent It will be observed that in both these instances the obsessing idea is one which is peculiarly repugnant to the patient's personality This is a common feature of all obsessions and will be found equally in obsessive impulses The latter are precisely similar in their nature to obsessive ideas except that here the patient is not merely impelled to dwell upon a thought but to carry out an action A mother for example is obsessed by an impulse to kill her children to whom she is passionately devoted Another patient has a constantly recurring impulse

During the first half of the nineteenth century a number of mental symptoms which could not be brought under any then recognized form of mental disorder were observed and recorded by various investigators These observations were independently made there was no clear recognition of any relationship existing between the conditions described and each was therefore treated as a separate clinical entity Thus there arose the monomanias of Esquirol corresponding mainly to the present group of obsessions the folie de doute the délire de toucher and other conditions belonging to the group now termed phobias Krishaber s syndrome, characterized by feelings of altered personality and so forth At a later stage a certain amount of coordination was carried out and the definite symptom groups of the obsessions and phobias emerged Magnan brought all these disorders under the conception of degeneracy regarding them as closely allied to the mental deficiency group but this view was unfruitful and at least in part certainly erroneous and until the advent of Janet no really consistent attempt at unification in a single entity was made

Janet observed that obsessions phobias states of hesitation and doubt and various other symptoms formerly described as independent entities tended to be associated together in one and the same patient and he devoted a prolonged study to these conditions with a view to discovering a common basis underlying them His investigations led him to conclude that all the disturbances in question were manifestations of a disorder to which he gave the name of psychasthenia and this conception elaborated in great detail in his *Les obsessions et la psychasthenie*" (1903) marks an important epoch in the history of the subject Although indeed, Janet s views would now be accepted in their entirety by only a few authorities we shall describe them at considerable length partly because his work is still the most comprehensive and complete exposition of these disorders at our disposal and partly because the subsequent task of explaining the divergent conceptions of more recent investigators will be considerably lightened if the reader has in mind the main points of Janet s conception

JANET S PSYCHASTHENIA

Symptomatology

Janet s psychasthenia is an extremely wide conception so wide that it may be said to embrace all the so called psychoneuroses except those which belong to the sphere of hysteria It includes therefore a great variety of symptoms which are classified by Janet in the manner shown in the accompanying table

actual achievement Thus a woman who has decided to purchase some potatoes for her husband's meal commences a soliloquy of this kind Shall I get them at A's shop or B's if I go to A the shop is likely to be very full and I shall be delayed so perhaps I had better go to B but the potatoes at B's are often inferior and I may meet my sister there and she will keep me talking there is a saleswoman at A's that I dislike and if he upsets me I shall not be able to cook my husband's dinner properly it is very important for his dinner to be all right today because he has not been well latterly" This rumination is continued perhaps for an hour or more during which time the task the patient is so anxious to accomplish makes no progress whatever It will be observed that rumination is closely akin to the manias recently described but in this case the compulsive mental process is diffuse instead of being systematized into a definite action or train of thought

Tics

Tics are constantly repeated systematic movements for example a regular stroking of the face with the right hand There are many varieties of tics and they occur in a large number of very different disorders Thus movements of this kind are met with in hysteria dementia praecox and other psychoneuroses and psychoses The psychasthenic tic however has certain features which enable it to be distinguished without difficulty The movement does not take place automatically and without the patient's knowledge as in the case of the hysterical tic On the contrary the patient's attention is fully absorbed in the carrying out of the action and it is accompanied by that same feeling of compulsion with which we have now become familiar The psychasthenic tic is indeed essentially identical with the manias already described and only differs in that the compulsive action consists in a simple movement rather than in a more elaborate procedure It is moreover often closely associated with a corresponding obsession or mania for example a patient obsessed with the idea that she is becoming fat feels constantly impelled to stroke her cheek to determine whether or not obesity is actually present a patient with a mania of precision consisting in a constant effort to ensure that everything belonging to her is in exactly its right place develops a tic like jerk of the head whose function is to assure her that her hat is placed at precisely the right angle

Crises of Motor Agitation

These are diffuse incoordinated movements accompanied by marked emotional tension and distress The states of emotional agitation termed by the laity hysterics with their shouts screams incoherent words irregular movements and jerks are typical examples of this condition

to commit suicide although he has no reason or desire to seek death Obsessive impulses of this type are common phenomena in psychasthenics and they present certain features which render their accurate recognition a matter of considerable practical importance The chief of these features is that although the patient feels the impulse to commit the act to be almost irresistible yet the act is hardly ever carried out In this respect the obsessive impulses are markedly different from the impulses to violence met with in epilepsy dementia praecox and other psychoses and the necessity of distinguishing them when the question of establishing measures of control and prevention arises is therefore obvious The distinction has to be made partly from the intrinsic character of the impulse itself partly from the accompanying signs indicating the existence of a psychasthenic or of some other condition

Manias

A mania is a train of thought or action which the patient persistently and repeatedly carries out in spite of its futility and irrelevance It is accompanied by the same feeling of compulsion observed in the case of the obsessions and although the patient fully appreciates the absurdity of the action its fulfilment seems to him to be an imperative necessity Mania is used here in practically the same sense as that in which we speak colloquially of a man having a mania for collecting stamps and has of course nothing whatever to do with the states of excitement occurring in certain mental disorders to which the name mania is also applied Manias may be of all sorts and kinds Thus we find manias of repetition in which the patient is irresistibly impelled to carry out the same action an indefinite number of times *e g* to return eight or ten times to the house when he leaves it in the morning to make sure that he has closed the front door ceremonial manias in which the patient is impelled to carry out some ceremonial before he undertakes whatever duty may await him *e g* to touch each object on the breakfast table twice before he sits down to his meal and so forth Minor examples of these phenomena are familiar to most of us in everyday life in the well known impulses to touch each lamp post or to walk only on the interstices between the paving stones

Rumination

Rumination is a phenomenon closely connected with the states of hesitation and doubt which will be subsequently described The patient when about to carry out some simple action commences an interminable train of thought which although more or less connected with the matter in hand wanders constantly into irrelevant byways and leads no nearer to its

of suffocation sweating and palpitation may be particularly mentioned The whole condition is of course intensely distressing and some notion of its peculiarly unpleasant character may be gained if we attempt to recollect the nightmares of our youth in which anxiety of this type forms an essential feature

Subjective Feelings of Deficiency (Sentiments d Incompletude)

These very characteristic phenomena consist essentially in a feeling on the part of the patient that his thoughts actions and emotions are inefficient inadequate and imperfectly carried out The subjective appreciation of inadequacy may extend to every mental operation and is often expressed in bizarre complaints whose real meaning the unskilled observer may find it difficult to understand

The underlying disturbance may be said to be a loss of selfconfidence which attaches itself to each and all of the patient s activities Thus in the sphere of action he may feel that whatever he does is inadequate and lacking in efficiency and adaptation to the need of the moment In the intellectual sphere he feels that his memory is unreliable that his attention is incapable of concentration and that his judgments are faulty The loss of selfconfidence extends even to his perceptions so that what he sees hears and touches seems somehow defective and illusory This last symptom is often expressed as a feeling of unreality attaching itself to everything in the patient s environment He will say for example that he knows that this is a table and that a chair but that they seem unreal and do not appear to him as a table or chair should appear The subjective feeling of deficiency may be manifested even in the patient s perception of him elf and he will complain that he has become altered in some mysterious way or he may endeavor to describe what he is suffering by some bizarre s atement *e g* that he is dead or that he feels as if he were leaving himself behind as he walks It is of course important to understand that in these cases there is no question of any actual delusions Lastly similar disturbances make their appearance in the sphere of the emotions and the patient complains that he is no longer capable of feeling any real affection or experiencing any true emotion

The patient s own estimate of his incapacities is always greatly exaggerated In spite of his assurance that his memory is unreliable his thinking powers crippled and his work grossly inefficient yet an objective examination shows that his memory is not notably impaired that he can carry out complicated trains of thought and that his inefficiencies are far less than he suppo es Nevertheless an actual objective deficiency in all these respects does exist

Phobias

A phobia is a fear experienced by the patient for some situation or object which does not in itself afford any adequate justification or ground for such fear A number of phobias have received specific names for example agoraphobia or fear of open spaces claustrophobia fear of closed places misophobia fear of dirt and so forth These names however have no real importance and it is more profitable to understand that a phobia may exist with regard to any situation or object We may have phobias of high houses of streets of country lanes of solitude of crowds of knives A patient afflicted with one of these phobias dreads intensely the corresponding situation or object and will take every possible precaution to avoid it

Phobias generally occur in close association with obsessions and manias and an enumeration of certain characteristic features which they possess will make clear how nearly they are allied to these other psychasthenic phenomena To begin with the patient fully appreciates that his fear has no objective justification and that it is indeed absurd This absurdity is all the more apparent both to the observer and to the patient in that the fear can be suspended by various in themselves obviously futile measures For example a patient who has a phobia of streets with high houses can traverse such a street with equanimity provided that he has a companion even if that companion is only a child of three He can also traverse it safely if he is allowed to hold on to the railings or even to wheel a bicycle Another patient with a phobia of railway trains can make a journey in comfort provided that he repeats to himself at regular intervals some meaningless formula (mania of conjuration) The second characteristic feature of a phobia is that if the patient is placed in the situation he dreads if in other words the phobia is transgressed he passes into that condition of intense emotional distress to which the term anxiety is applied and which will be fully described below This condition may become so pronounced that the patient falls down in a state of collapse It is to be noted that anxiety of this type is also produced if a compulsive action (mania) is frustrated

Anxiety

Anxiety is a term that has become debased and generalized in English so that one speaks for example of a man being anxious to have his dinner It is used here however to designate a peculiar emotional state more precisely denoted by the French "angoisse or the German Angst This state is characterized by both mental and physical symptoms the former consisting in tension unrest terror and apprehension and the latter in various visceral sensations among which tightness in the chest with a feeling

ences considerable difficulty in responding to it His energies moreover instead of grappling with the task required tend to flow over into a series of activities which serve no useful purpose and only hinder the accomplishment of what is really necessary These futile activities constitute the compulsive phenomena Thus a patient proposing to purchase potatoes for her husband s dinner instead of promptly carrying out the necessary actions passes into a prolonged phase of rumination of the kind described in a former paragraph or she returns repeatedly to the front door to assure herself that it is shut (mania of repetition) or she feels impelled to carry out an interminable series of ceremonial actions before she can venture forth or she exhibits some phobia or obsession or finally she abandons the task as insuperable and dissolves into a crisis of motor agitation The situation may be summarized by saying that the primary action (the task required) is not carried out but there is substituted for it a series of secondary actions all of which are futile and sterile

It is to be noted that it is not the inherent difficulty of the primary action which overwhelms the patient He may be quite incapable of carrying out some simple duty demanded by everyday life although able to accomplish with ease an elaborate train of abstract reasoning which has no immediate relation to concrete needs We may find indeed astonishing paradoxes of this kind for example a patient who when she is requested to add up the current household account for presentation to her husband breaks down at once into hesitation doubts and manias but who can add up without difficulty a precisely similar column of figures which she believes to have been put down at haphazard and without relation to actual requirements

The explanation of these apparent inconsistencies lies in the fact that the psychasthenic patient s essential difficulty is adaptation to reality the reality of the present moment with its demand for a corresponding adjustment of thought and action It is not an intellectual deficiency in the sense in which this term is commonly understood Hence the patient finds the simple affairs of everyday life insuperable although he can carry out trains of abstract thought or imagery which are intrinsically vastly more complex Janet endeavors to explain these facts by the assumption of the existence of a function of reality " which is normally an unnoticed component of our activities but which is lacking or inadequate in the psychasthenic and in pursuance of this conception he has drawn up a hierarchy of mental operations graded according to the extent to which they require the presence of the function of reality At the summit of the hierarchy is efficient action thought and emotion adapted to the requirements of the present moment beneath this comes abstract reasoning imagination and revery without precise relevance to the present situation and at the bottom are non adapted

Actual Psychological Deficiencies (Insuffisances Psychologiques)

These are found in just those activities of which the patient complains although their objective magnitude is considerably less than he believes Thus in action the patient will be found to be irresolute lacking in decision and hesitating awkward in achievement and markedly timid especially in his social relationships In thought he will be found to be defective in attention and with a notable tendency to wander off into vague reveries a phenomenon which in its more marked forms becomes the rumination we have already described In the sphere of emotion he will be found to display either indifference or an exaggerated emotivity Lastly his subjective feelings of indecision and lack of emotion lead him to seek constantly for compensation Hence he craves for someone to decide for him and to reassure him (need of direction) and for someone to whom he may give affection and from whom he may receive it

Physiological Disturbances (Insuffisances Physiologiques)

Janet includes here a number of symptoms such as headache backache disturbances of the digestive and other organs which he regards as the result of nervous exhaustion Although these no doubt occur in psychasthenic patients it is very doubtful whether they properly belong to the syndrome now under discussion and they will not therefore be further described here

General Characters of Psychasthenia

It will be observed that in the table on page 1047 the phenomena of psychasthenia are divided into two main groups compulsive phenomena comprising compulsive ideas and processes and stigmata comprising the subjective feelings of deficiency and the actual deficiencies The broad line of distinction between these two groups is that the symptoms belonging to the second are more or less constantly present although varying from time to time in degree whereas the symptoms belonging to the first only occur occasionally and only under special circumstances That is to say the patient is always more or less irresolute doubting hesitant lacking in self confidence and conscious of his deficiencies but that only under certain conditions does he exhibit obsessions manias phobias or other symptoms belonging to the first group These conditions consist essentially in the patient being called upon to carry out some action or definite train of thought demanded by the needs of the moment This need may be of the simplest kind but so long as it calls for a definite adaptation of the patient s thoughts and actions to the requirements of the actual situation he experi

Janet subdivides psychasthenia into two varieties, the constitutional and *the acquired. The former is characterized by a marked neurotic heredity,* appearance at an early age and by the absence of any grave mental or physical disturbance preceding the onset. Its course is chronic, although with variations in intensity, and the prognosis as regards complete recovery is very unfavorable. In the acquired variety heredity is comparatively slight, the disorder may make its appearance at any age and there is generally a history of some illness, shock or severe stress preceding the onset. The course may be short and the prognosis is much more favorable.

Criticism of Janet's Conception of Psychasthenia

It has been observed that Janet incorporated in his conception of psychasthenia a great number of conditions formerly treated as independent entities and sought to show that they were all merely different manifestations of one and the same essential disturbance. He included in it, moreover, those cases showing physical symptoms—headaches, functional disturbances of the digestive and other organs, and so forth—which had usually been classified under neurasthenia and which were at that time regarded as a result of nervous exhaustion. Practically Janet divided the whole *field of the neuroses into two areas and held that all those disturbances which* did not belong to hysteria were manifestations of psychasthenia.

Now, although Janet's generalization was undoubtedly of great value, subsequent investigators are almost universally agreed that it is too sweeping and that he has endeavored to gather into a single net a number of conditions which cannot profitably be so treated. Cases accurately corresponding to his conception with well marked stigmata and frequently recurring obsessions, phobias, manias and other compulsive phenomena unquestionably occur and when met with present a very characteristic picture. But that individual symptoms may occur in other settings and as a part of psychoneurotic disorders which have nothing to do with a general psychasthenic condition seems to be beyond question. For example, those physical disturbances which Janet regards merely as physiological manifestations of psychasthenia are without doubt of psychogenic origin, but they often arise independently and in patients who do not show in the least the typical reaction of the psychasthenic. Anxiety, again, that peculiar state of terrified apprehension which Janet includes as an integral part of psychasthenia, seems to occur in many other conditions and our experience in the War has shown that it, or a very closely allied state, is a common feature of war psychoneuroses which have otherwise nothing in common with psychasthenia. The same thing applies to some extent to obsessions and phobias.

thoughts emotions and actions of the type seen in the compulsive phenomena of psychasthenia Janet s view is that the psychasthenic is able to carry out the operations belonging to the lower degree of the hierarchy which make less demand upon the function of reality but fails at those belonging to the higher degrees He considers moreover that the patient s command of the function of reality varies from one time to another so that he is sometimes able to perform operations belonging to a degree in the hierarchy to which at other times he cannot attain This corresponds of course to the well known clinical fact that the patient s mental level as Janet terms it varies from time to time so that at one period his behavior is comparatively normal while at another he is able to accomplish nothing Finally Janet conceives that the particular conditions referred to in a preceding paragraph which lead to the exhibition of various compulsive phenomena consist essentially in a demand for an action train of thought or emotion requiring a higher coefficient of the function of reality than the patient possesses at the moment As a result the task cannot be performed but the patient s energies diffuse themselves in activities belonging lower in the hierarchy and the various compulsive phenomena thus make their appearance

Janet s conception of a hierarchy in which the various mental operations are placed in an order very different to that usually assigned to them is of great interest It corresponds in spite of the currently accepted estimate of the superiority of feats of abstract reasoning and imagery in comparison with the simple mental processes required to deal with the emergencies of every day life to a standard by which in practice we tend universally to judge our fellow men It is according to this standard that we feel admiration for the man of action and contempt for the dreamer respect for the man who does things kindly tolerance for the professor and dislike of the academic The same standard in the affective sphere gives us contempt for sloppy and diffuse emotion but profound respect for strong and adapted emotion It must be understood of course that abstract reasoning closely directed to a definite goal and imagery controlled for a certain end the reasoning and imagery of a Newton are mental operations with a high coefficient of the function of reality and naturally belong to the summit of the hierarchy

Janet s conception of the nature of psychasthenia is then that it consists essentially in a diminution of the capacity of the mind to adapt itself to the requirements of reality with a tendency to react to these requirements by a characteristic disintegration into various futile processes which constitute the symptoms of the disorder He regard hysteria as due to a precisely similar failure of adaptation to reality but with a tendency to react by a different form of disintegration leading in this instance to the appearance of functional anesthesias and paralyses amnesias somnambulisms and so forth

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but in most of these cases careful investigation does as a matter of fact disclose a long history of signs and symptoms showing a typical psychasthenic reaction preceding the appearance of the obsession or phobia

Now the cases which correspond accurately to Janet s conception which show both the characteristic stigmata and numerous compulsive phenomena will generally be found to belong to his constitutional type That is to say they have shown the typical psychasthenic reaction from an early age and a constant succession of psychasthenic symptoms throughout their life history Those questionable cases on the other hand where individual symptoms are found in other settings and independently of any obvious general psychasthenic reaction belong in most instances to Janet s acquired type

We may therefore tentatively adopt the following position Constitutional psychasthenia may be accepted as a definite clinical entity which Janet has carved out from the mass of the psychoneuroses and which we shall find to be of the greatest value in its diagnostic prognostic and therapeutic aspects Janet s contention however that all the symptoms of the neuroses other than the hysterical belong to psychasthenia cannot be supported and his acquired type is probably made up of a number of quite independent conditions

There is no general agreement however as to the number or delimitation of these conditions and the many divergent schools which now exist put forward classifications differing from one another in the most fundamental respects It must be clearly understood moreover that even the conception of constitutional psychasthenia which we have tentatively accepted above is not recognized by certain of these schools as constituting a definite clinical entity The whole question of the nature relationship and classification of the various psychoneurotic symptoms which Janet grouped together in his psychasthenia is in fact at present far from the attainment of any stable solution and is still a subject of considerable dispute The various conceptions proposed by modern authorities are indeed so numerous and diverse that it would be quite impossible to discuss them within the limits of this article We shall therefore content ourselves with a description of the views of the two writers whose theories and practice are most widely accepted Déjerine and Freud

Déjerine s Conceptions

Dejerine accepts Janet s constitutional psychasthenia as a definite entity but he considers it to be essentially different in its nature from the psychoneuroses and to belong to the group of the psychoses He altogether excludes it moreover from the sphere of application of psychotherapy at

any rate that form of psychotherapy which he advocates for hysteria and neurasthenia The various physical disturbances which Janet has incorporated in his psychasthenia together with a number of the mental symptoms belonging to the subjective feelings of deficiency group Déjerine separates altogether regarding them as manifestations of neurasthenia He limits the term psychoneuroses to neurasthenia and hysteria and excludes psychasthenia from it That is to say he maintains that neurasthenia and hysteria are psychogenic disorders but that Janet s constitutional psychasthenia is not

Freud's Conceptions

The conceptions introduced by Freud of Vienna constitute without doubt the most important contribution to psychopathology which has yet been made This importance is mainly dependent upon the fact that they offer a dynamic explanation of psychological phenomena that is to say they explain the phenomena as the result of definite forces working according to definite laws and do not merely attempt to analyze mental processes into their constituent elements Incorporated in these conceptions and indeed forming the kernel from which the more general conceptions have developed is a theory of the etiology and nature of the psychoneuroses including those symptoms which Janet has brought under the head of psychasthenia It is not possible however to understand Freud s views with regard to these symptoms without some knowledge of his general conceptions of the nature of psychological processes and we shall therefore attempt to give a very brief description of his fundamental principles before passing on to that portion of his work which directly concerns the subject of this article

Freud regards mental activity as the result of the action and interaction of forces which ultimately derive their energy from the fundamental instincts existing in the mind These forces may either work harmoniously together or two or more of them whose activities are discrepant or incompatible with one another may be simultaneously excited In the latter case a state of conflict arises characterized by a peculiar emotional tension and a paralysis of action A state of this kind cannot persist indefinitely and it is necessary for some solution of the conflict to occur Various solutions are possible the conflict may for example be resolved by a deliberate and conscious adjustment of the opposing forces or it may be evaded by some means This evasion is commonly effected by a process of repression One of the opposing forces is repressed or shut out of consciousness so that it is no longer permitted to exercise its normal activity of influencing the stream of consciousness in a direction which subserves its ends The repressed force

does not thereby cease to exist, but passes into the unconscious levels of the mind where it continues to exert an effect on consciousness although an indirect one It is in these indirect effects of repressed psychic forces that Freud finds the explanation of the symptoms of the psychoneuroses A psychoneurotic symptom is for him the expression of a psychic force which has been repressed into the unconscious because it is incompatible with the other forces which dominate consciousness and which is only able to make its appearance in an indirect and distorted form owing to the resistance exerted by these other forces An example taken from one of Freud s earlier works will help to make clear the nature of the mechanisms which have just been described A patient was constantly troubled by a subjective sensation of smell resembling burning pastry which occasioned her considerable distress but which she could not explain Investigation showed that two months previously an episode of a highly emotional character had occurred and at the time in question it happened that some pastry which was being cooked in the room became burnt On account of its painful character the memory of the episode was repressed and shut out of consciousness and it had apparently disappeared from the patient s mind It contrived however to affect consciousness indirectly by introducing therein an element only connected with the real traumatic episode by a chance contiguity the smell sensation It will be seen that in this way the repressed system is able to achieve expression but only by undergoing an amount of distortion sufficient to render its real origin and significance unrecognizable to consciousness This distortion may be effected in many different ways and according to the particular process selected depends to a considerable extent the type of psychoneurosis which results Thus the repressed system may make its appearance by the production of some physical symptom as in the anesthesias paralyses and so forth of hysteria Or again it may manifest itself by attaching to some indifferent idea or process the emotional elements belonging properly to the repressed system In this case there results in consciousness an obsession or obsessional process

The conceptions of conflict and repression and the various modes in which repressed systems may influence consciousness and produce psychoneurotic symptoms have been investigated by Freud in great detail and the work which he has carried out along these lines has exerted a profound effect on the development of modern psychopathology His views with regard to the mechanism of production of psychoneurotic symptoms are in their essentials at least becoming more and more widely accepted and they provide the most comprehensive and satisfying explanation of these phenomena which is as yet at our disposal With regard to another section of Freud s work however opinion is much more divided This section comprises his theories with regard to the nature significance and action of sex

Freud maintains that the forces concerned in the production of the psychoneuroses are in all cases when analyzed into their ultimate components found to be sexual in character He conceives that the forces of sex to which term he give an unusually wide significance make their appearance very early in life and that in the initial stages they comprise a number of components which cannot be distinguished in the sexual constitution of the adult These components include autosexual and homosexual tendencies The sexual constitution of the normal adult develops from these infantile components by a process of selection and suppression and it is in a failure of this normal development that Freud finds the essential condition for the origin of a psychoneurosis That is to say he believes that the psychoneuroses arise because the infantile sexual components do not undergo a normal suppression and diversion of their energy and there hence arises conflicts between the individual components on the one hand and between the components and the other forces of the mind particularly those arising from education and tradition on the other hand From these conflicts and the repressions which result from these conflicts the symptoms of the psychoneuroses arise in the manner already described

Freud's Classification

Freud does not accept psychasthenia as an entity and the term finds no place in his works He divides up the various symptoms which Janet has brought together in his conception of psychasthenia along quite different lines of section distributing them mainly amongst the conditions which he names anxiety neurosis anxiety hysteria and compulsion neurosis

Anxiety neurosis is characterized by the presence of that morbid anxiety whose nature has already been described Freud regards this symptom as invariably due to the arousal of sexual excitation which is not permitted to pursue its natural course toward the attainment of normal gratification It is a consequence for example of the practice of coitus interruptus In anxiety neurosis this symptom occurs practically in isolation but it is also met with combined with other symptoms in anxiety hysteria and the compulsion neurosis

Anxiety hysteria is a form of hysteria in which the symptoms are predominantly mental as opposed to that form (conversion hysteria) in which the symptoms are predominantly physical (anesthesias paralyses and so forth) Many of the cases showing anxiety and phobias are classified by Freud in this group His view of the essential mechanism underlying hysteria is that it consists in a repression of one or more components of the sexual instinct owing to these components being in conflict with other forces existing in the mind The symptoms arise as a result of the inter

action between the repressed components and these other forces whereby the former achieve some expression in consciousness but only in a distorted form (compromise formation)

Compulsion neurosis includes those cases in which obsessions manias and certain phobias occur and corresponds closely to Janet s constitutional type of psychasthenia Freud regards the mechanism here as essentially similar to that of hysteria except that in this case the repressed component achieves expression by attaching its emotional force to some indifferent idea or process (displacement) Hence there arises an obsession mania or other compulsive phenomenon which owes its apparently irrational and futile character to the fact that the driving force attached to it really belongs to some other repressed mental element Freud s views on the nature of the compulsion neurosis have undergone considerable change and development and it is not possible to give any adequate description of them within the limits of this article Reference should be made to the numerous works of Freud and his school

General Remarks

It will be apparent that the various symptoms constituting the subject of the present article are very differently regarded by different authorities both as to their nosological relationships and as to the nature and causation of the processes responsible for their origin These divergent views are inevitably a source of considerable confusion to the practitioner and it will therefore be profitable to lay down a position which he may take up with regard to these cases so that he may form conclusions as to the all important questions of prognosis and treatment without confining himself to the tenets of any particular school The remarks in this and the succeeding section are an attempt to achieve this end but it must be clearly understood that the conclusions reached are tentative in character

In the first place the cases corresponding to Janet s constitutional type of psychasthenia form a fairly well marked clinical group which can be recognized with ease These are the cases which have shown throughout their life characteristic stigmata lack of self-confidence subjective feelings of inadequacy states of hesitation and doubt and a constant difficulty in adjusting themselves to the claims of reality while at interval obsessions manias phobias and other compulsive phenomena have made their appearance

The prognosis here is obviously bad so far as recovery is concerned and in all probability the disease will continue to follow the course which it has already pursued for years that is to say the stigmata will persist and

compulsive phenomena will manifest themselves from time to time although their intensity may vary considerably and there may be prolonged periods during which the patient is comparatively free from them Nevertheless it may be said that although the psychasthenic symptoms will be more or less permanent and may at times become very acute there is but little chance of the condition progressing to a definite insanity This is an important point because both the patient and his relatives often have a lively fear of this contingency and it is very necessary to reassure them with regard to it With regard to treatment it is extremely questionable whether in the present state of our knowledge any real radical cure is possible but much may be done by palliative measures along the lines which will be described below

The cases with physical symptoms of psychogenic origin headaches digestive disturbances and so forth those with subjective feelings of inadequacy and objective deficiencies not associated with the general clinical picture of constitutional psychasthenia described above and the cases in which anxiety phenomena dominate the clinical picture although included by Janet in his conception of psychasthenia cannot profitably be considered therewith either as regards prognosis or treatment and should be dealt with separately

Cases in which obsessions or phobias are met with in comparative isolation and without the general setting and long preceding history of constitutional psychasthenia seem to occur but probably with a frequency much less than might be supposed In the greater number of cases apparently belonging to this type careful investigation will disclose the presence of long standing stigmata and previously occurring compulsive phenomena which have not been elicited by a superficial examination In so far however as evidence of the constitutional condition is not forthcoming the prognosis is relatively good and the prospects of achieving satisfactory results by treatment relatively favorable

It may be of interest to point out that although a large number of psychasthenic cases were naturally met with in the army during the war psychasthenia is not in any sense a specific war neurosis The majority of the cases were merely instances of constitutional psychasthenia of long standing in which an exacerbation had been produced by the stress of military service The obsessions and other symptoms were of course colored by the particular character of these stresses In a limited number of cases obsessions and phobias occurred apart from a pronounced general psychasthenic condition corresponding to the clinical group described above Only in these cases could the peculiar psychological conflicts associated with war conditions be said to have played an essential part in the causation of the disorder

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mind but in this case the end is achieved by a process of logical argument so that the conviction is accepted because the patient sees that it is necessarily true Reeducation is a method whereby the morbid mental processes are gradually trained to pursue a normal course For example reeducation may be applied to a phobia a patient with a phobia of streets being instructed to accustom himself firstly to stand for a moment outside his house then to walk a few yards down the street and so on

Psychoanalysis is the method devised by Freud both for the investigation and treatment of psychoneurotic disorders Its object is to discover the various forces whose conflict and unconscious action are held to be responsible for the condition and then to adjust these forces so that the morbid effects are no longer produced The procedure employed consists essentially in requiring the patient to communicate freely whatever thoughts may happen to pass through his mind the physician then deducing from the material thus provided by the aid of his knowledge of the mechanism of mental processes the unconscious elements whose conflict has produced the symptoms The method involves a complicated and elaborate technique which cannot be described here and for which reference should be made to the various special works on the subject

Analytical methods of treatment that is to say methods whose object it is to elucidate the causes responsible for the morbid condition and then to remove the condition by removing or adjusting these causes are employed by many physicians who do not accept Freud s theories in their entirety *But almost all of them are based in whole or in part on Freud s work and* accept the fundamental postulate that the symptoms are the result of conflict between emotional or instinctive forces

We may now review the applicability of these various methods to the disturbances with which we are here concerned and to begin with we may consider the possibilities of treatment in that clinical group which we have separated out as *constitutional* psychasthenia corresponding mainly to Freud s compulsion neurosis It is claimed that in these cases psychoanalysis offers a prospect of radical cure but it is admitted that the result is uncertain that the technique is difficult and that the treatment must necessarily be very long extending perhaps to two or three years and therefore involving a great expenditure of time and money It must in any case only be attempted by an experienced psychoanalyst because unskilled intervention along these lines may not only fail to do good but may be productive of very considerable harm

Although no other method offers even a prospect of radical cure much may be done by palliative procedures and perhaps the most satisfactory of these is the treatment which Janet himself devised and to which we may give the name of director method This method really depends upon the utiliza

Treatment of Psychasthenia

The question of the treatment suitable for the disorders dealt with in the present article is naturally dependent upon the view adopted with regard to their nature and etiology and is therefore a subject of considerable dispute among the various schools of thought now existing It seems probable however that almost all the measures proposed have some utility and we shall therefore shortly review the methods available, and then proceed to consider how far they are applicable to the cases with which we are concerned

Physical methods of therapeutics drugs and so forth are at any rate in the present state of our knowledge useless It is possible that future investigation will elicit a physical basis on which constitutional psychasthenia is developed and endocrinology seems especially to promise some ultimate illumination in this direction but at the moment no practical results are available The popular method of the rest cure often indiscriminately applied to all types of functional nervous disorder is certainly not to be recommended in these cases and is likely to do far more harm than good The only treatment which can be employed at present is psychotherapy and several psychotherapeutic methods have been used with some measure of success The available methods are suggestion persuasion reeducation psychoanalysis and the various analytical procedures based to a greater or less extent upon psychoanalysis Each of these methods will be shortly defined and their applicability then discussed

Suggestion consists in the introduction into the patient s mind of an idea or rather conviction which tends to inhibit or modify the morbid mental processes The introduction is effected by making use of the personal influence of the physician or of some other extraneous agent and without attempting to establish any logical basis for the acceptance of the conviction Thus it may be effected by simply stating the proposition to the patient and relying for its acceptance upon the patient s belief in the authority of the physician or it may be effected by the employment of some agent which increases the patient s suggestibility or which he has been taught to regard as capable of immediately producing the desired effect such as hypnosis the suggestive use of electricity etc An attempt is made for example by one or other of these means to suggest to the patient that he will no longer experience a certain obsession and if the suggestion is successful the appearance of the obsession is thereby inhibited Janet s "director method which will be described below is to be regarded as a special form of suggestion

Persuasion is also a method of introducing a conviction into the patient s

CHAPTER XXXVII

OCCUPATION NEUROSES

By PERCY SAUNDERS

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GENERAL DESCRIPTION

The occupation neuroses or craft palsies constitute an ill defined group of affections in which a functional disability in the performance of certain more or less skilled movements arises as the result of the repeated and prolonged use of these movements in the course of the patient's work. He becomes unable to carry them out properly or in some cases to do them at all although he may still be able to use the particular muscles involved quite well for other purposes. In many cases the disability is associated with the development of cramps and involuntary spasms in these muscles whenever the patient attempts to perform the movements that are at fault and the occupation neuroses are frequently referred to therefore as professional cramps we speak of writer's cramp telegraphist's cramp violinist's or pianist's cramp and so forth. Other factors besides cramp however contribute to the disability and there are many cases in which no cramp is present or in which it is late in appearing so that the term occupation cramp although it has become established by long usage must be regarded as less applicable to the condition as a whole than the broader designation occupation neurosis

tion of one of the symptoms of the disorder the need of direction which we have described as one of the actual psychological deficiencies of psychasthenia The patient is unable to adapt himself to the demands of life and feels a constant need for someone who will direct him as to the course he should take decide his problems resolve his hesitations and so forth The director method consists in the deliberate adoption by the physician of these functions in relation to his patient It is not necessary that he should be always at hand for this purpose but only that he should be available when the patient s mental level is low and the problem of adaptation is found to be insoluble When such a period occurs the crisis can be successfully tided over provided that the patient has acquired the necessary confidence in the physician and that the latter reassures the sufferer as to his doubts and hesitations and decisively indicates the course to be pursued By these means it is often possible to preserve the patient from acute exacerbations and to enable him to lead a comparatively normal life It must be always remembered that decision must be the keynote of the physician s attitude that he must display no doubts himself and that he must avoid thrusting the responsibility for any choice of action upon the patient It is recorded that a psychasthenic patient has been plunged into an emotional crisis because the physician informed him that for treatment of rheumatic symptoms he could go either to Bath or Harrogate The result was a long series of doubts and ruminations concerning the possible merits and demerits of these two places culminating in a crisis of emotional agitation

In addition to these general measures individual symptoms can be dealt *with by one of the psychotherapeutic methods described above* Suggestion may be used for treatment of obsessions and phobias but the results are rarely satisfactory It is seldom possible in these patients to attain any adequate degree of hypnosis Persuasion is generally useless Reeducation is often a useful palliative measure in dealing with obsessive actions and phobias the patient being taught very gradually to curb the action or to accustom himself to the position which arouses the phobia The most efficient method however of dealing with an obsession or phobia is by some form of analytical treatment The various forces whose repression and conflict have produced the individual symptom are elucidated and an endeavor made to adjust them and to subject them to the deliberate control of consciousness The procedure involves an expert knowledge of morbid mental mechanisms and can only be carried out by a skilled psychopathologist

Those cases in which obsessions or phobias are met with in comparative isolation in which the history is short and in which the general signs of constitutional psychasthenia are but little in evidence offer an excellent promise of success to efficient treatment Treatment here should always be conducted mainly along analytical lines aided by suggestion and reeducation

of muscles are carried out in frequent repetition for considerable periods of time The upper extremity is more often involved than the lower and those occupations requiring the performance of fine precise movements of the hands give rise to neuroses more readily than those in which the use of larger muscles is involved while those requiring delicate unilateral hand movements seem to be especially liable to cause the affection and hence one reason why writer s cramp has become the type of the condition The occurrence of the affection is not limited however to such occupations for it may be found occasionally in workers who use the large muscles of the trunk as in sawyers and occasionally too it may involve the movements of cranial nerve muscles as in some of the occupations already mentioned

The great majority of the cases are seen in patients between the ages of twenty and fifty Of the eighty one cases mentioned above four began before the age of twenty and eight after the age of fifty while the remainder were about equally spread over the three decades between twenty and fifty The frequency of the condition in the two sexes varies according to the extent to which different occupations are followed by men and women but on the whole one sex seems about as liable to it as the other Writer s cramp is much more common in men than in women but men until recently have been much more engaged in pursuits that lead to it for it is especially apt to occur in lawyers clerks bank clerks and bookkeepers who have to write in small cramped space or make out reports of figures in narrow columns Telegraphist s cramp according to Thompson and Sinclair s investigations occurs usually at an earlier period of service in women than in men Most of their cases seem to have been in men Amongst the cases at the National Hospital already mentioned forty seven were in men and thirty four in women The number of writer s cramp cases in this series was twenty four in men and twelve in women the number of cases other than writer s cramp was therefore nearly equal in men and women and of these there were eight cases of telegraphist s cramp in men and eight in women

ETIOLOGY

In most cases the disability comes on slowly in the course of years of work at the particular occupation The average length of service before telegraphist s cramp developed in the series of thirteen cases studied by Thompson and Sinclair was sixteen years and varied from six to twenty eight years Severe writer s cramp usually comes on in professional writers after many years ten fifteen or twenty of writing day after day A patient with button holer s cramp was said to have worked at button holing ten and a half hours a day for twenty years A box maker

Occurrence

The affection may occur in a great number and variety of pursuits and almost every occupation has its neurosis Writer s cramp is the best known example of the condition but instances of it are found in such diverse occupations as that of telegraphy sewing button hole making piano playing violin playing flute playing hammer work, gold beating blacksmith s work shaving sawing, milking dancing treadle working weaving box making steel polishing letter sorting pedal working cigar making cigarette rolling bricklaying typesetting and many others The condition known as "tennis elbow belongs frequently to these disabilities Meat inspectors may develop a neurosis from the constant use of a microscope and watch makers from the continuous holding of a magnifying glass in the eye Miner s nystagmus belongs to these occupation affections also while a neurosis has been described in trumpet blowers and cornet players and occasionally in public speakers and preachers

Although the affection occurs in so many different occupations it is not on the whole a very frequent condition Telegraphist s cramp is one of the most common instances of it after writer s cramp and in their statistics of 7 465 persons engaged in telegraphy Thompson and Sinclair found 417 in whom there was difficulty in sending messages due either to actual cramp or to the early subjective sensations of the affection and in 148 telegraphists personally examined by them there were 7 with true cramp and 6 in the early subjective stages of the condition In most of the occupations that have been enumerated however and in many others that might be mentioned it is very rarely that a true neurosis occurs of the type with which the study of writer s cramp and telegraphist s cramp has made us familiar and in some occupations the condition has been of the nature of a medical curiosity

Of eighty one cases of occupation neuroses of various kinds at the National Hospital Queen Square in the last few years thirty six were cases of writer s cramp sixteen cases of telegraphist s cramp four cases of typist s cramp, two of pianist s cramp and two of violinist s cramp In addition to these writer s cramp was combined with telegraphist s cramp in five cases with typist s cramp in one case with violinist s cramp in one case and with needle cramp in one case and telegraphist s cramp with pianist s cramp in one case while the remaining twelve cases were for the most part single instances of the affection occurring in various other occupations

It would seem that the occupations most likely to give rise to the condition are those in which more or less complex movements acquired by education and practice and necessitating the coordination of various group

myelitis may be found associated with an occupation neurosis and in the case of the upper extremities supernumerary cervical ribs are sometimes present as a complication These local conditions have been thought to predispose to the development of the neurosis but it is very doubtful if they play very much part in the production of a true neurosis condition Cases occurring in association with them however are sometimes classified as secondary occupation neuroses

Certain other special causes arise for consideration sometimes in connection with different occupations In some occupations the excessive speed with which particular movements have to be carried out may be supposed to help in causing the affection but although frequency of repetition must be an important element in rendering the performance of movements excessive it is a much less common factor in causing the overstrain of occupation neurosis than the character and complexity of the movements themselves and the way in which they are carried out In many occupations where speed is of great importance a neurosis is rare and even where it seems to contribute to the development of the condition as in telegraphy other factors are probably more important The average speed of fast typewriting requires several hundred contractions of the muscles a minute although probably less than fast telegraphy Typewriter s cramp is however comparatively rare The finger movements in typewriting are bilateral and much freer and more varied in character than in telegraphy key work in which alternate flexion and extension movements of the fingers and hand are chiefly required with variations in the pressure employed for the dots and dashes of the signal Gowers noted the fact too that shorthand writers rarely develop cramp in shorthand writing notwithstanding the speed with which they work This he explained as due to the fact that their speed compels them to a freer muscle play than the ordinary longhand writer so that they use the arm muscles more and the small hand muscles less

In some occupations indeed a faulty technique in the carrying out of the particular movements required is probably an important contributory cause of the neurosis Gowers laid special stress on it as a cause of writer s cramp Such things as writing sending in telegraphy and many other occupations requiring the use of the fingers necessitate movements of short excursion and graduated strength at distal parts of the limb and there is a tendency in certain faulty methods to make these movements entirely at the distal joints the rest of the arm being kept fixed This brings into excessive use the more distal and smaller muscles of the limb and leads to their overstrain in a cramped excursion A neurosis is much less likely to develop in these occupations if the arm is kept less fixed and rigid and the play of movement that is required made more with the larger muscles of the limb and probably

developed a cramp in using his hammer after fifteen years at his work In other patients however certain varieties of the complaint may develop comparatively quickly after short periods of more or less excessive work beyond their capacity to bear as in a patient with writer s neurosis in whom the immediate onset of the trouble was due to her having to address several thousand envelopes and imitate someone else s handwriting in doing so The actual amount of work that brings on the neurosis varies very much there fore in different cases and various accessory factors besides the mere repe tition of the occupation movements may contribute very largely to its causation

In many cases the nervous temperament of the patient plays a very considerable part in predispo ing him to the development of the affection and nervous and mental factors enter largely into its etiology The affection occurs for the most part in patients of unstable nervous temperament who are prone to develop neurasthenia and other functional nervous complaints and so frequently is this neuropathic tendency found in the subjects of occupation neurosis that it must be regarded as a most important factor in the causation of the condition In many cases too business and domestic worries and anxieties are present or various conditions of ill health and these tend to lower the patient s powers of nervous resistance and contribute to the development or aggravation of the disorder while in other cases the monotony attached to certain forms of work may have a mental effect quite apart from a physical one in predisposing to the development of the neurosis In still other cases various mental complexes or emotional disturbances associated with the patient s occupation seem to be the exciting cause of the trouble

These mental and nervous elements vary very much in importance in different patients and even in different occupations In the wide class of patients liable to develop writer s cramp they are often more noticeable than in the smaller class of picked workers subject to telegraphist s cramp or other more specialized disability In some varieties of the affection too such as the very slowly developing cramp cases they seem sometimes comparatively unimportant but in occupation neurosis as a whole they must be regarded as most important factors along with the excessive use of the occupation movements in bringing about the condition while in some cases they become the chief cause the neurosis may be traced to a shock or fright or emotional disturbance or mental complex associated with the patient s work or may be present only under certain conditions of mental or nervous stress and excessive performance of the occupation movements at fault judged by ordinary standards is altogether lacking

Other contributing factors are sometimes found in various local affections of the limbs Conditions of chronic arthritis recent injury or old polio

In ordinary writer s cramp in the strict sense the motor symptoms constitute the most characteristic features of the condition Sometimes they develop slowly and insidiously by themselves but in most cases they arise in association with feelings of aching and fatigue in the hand and arm and especially in the fingers and wrist that the patient has begun to find accompanying his writing at longer or shorter intervals after he takes up the pen while throughout their course they are usually attended to greater or less extent by sensations of discomfort and even pain in the muscles and joints of the limb In their earlier stages they are often somewhat indefinite in character At first there may be merely an awkwardness and stiffness in writing and the patient has some difficulty in coordinating the movements of his fingers properly as the condition becomes more established this difficulty gradually increases he seems to have le s and less control over his muscles whenever he goes to use them for writing a weakness or stiffness develops in his fingers or actual spasm and involuntary contractions occur in them as he writes and interfere with the freedom of their movements His writing becomes slower and altered in character the letters are slurred over or cramped and small or variable in size or too few or too many strokes are put in here and there he digs his pen into the paper involuntarily every now and then and does not seem able to keep his fingers on it to hold it properly and keep it steady although it often appears to him that he is really grasping it very tightly He tries holding it in different ways between his fingers or sometimes even clasping it tightly in the palm of his hand but after a short time one way of holding it does not seem any better than another and if writing is persisted in the condition get gradually worse while in some of the advanced cases the movements of the wrist and even of the arm and shoulder become affected as well as tho e of the fingers and the patient becomes quite unable to control his pen to write at all

The classical description of the affection recognizes three different varieties of the condition according to the predominant motor symptoms present in different cases the spasmodic or spastic the tremulous and the paretic Of these three varieties however the spastic or spasmodic is by far the most important and the majority of cases of the affection belong to it while the tremulous and paretic varieties are exceedingly rare in anything like pure form although tremor and various degrees of paresis or weakness may be present to greater or less extent in association with the spastic symptoms of the spasmodic variety In many case indeed the motor condition is a very mixed one and various elements of weakness spasticity and mal coordination enter into its production

The spasmodic cases are characterized chiefly by the occurrence of spastic phenomena of excessive contraction overaction and involuntary spasm in the muscles beginning usually in the muscles that hold the pen

similar considerations of technique apply in regard to the movements in many other occupations also

Somewhat similar causes are found in the use of faulty instruments or in working under improper conditions Hard steel pens at one time were supposed to be responsible for the development of writer s cramp because they necessitated greater pressure and therefore firmer contractions of the hand muscles The use of very small penholders also sometimes aggravates the condition In telegraphy the use of the Morse key type of instrument seems more often to lead to telegraphist s cramp than that of the Baudot or Hughes Bad desk accommodation also with insufficient room to rest the arm properly may be partly responsible for causing writer s and telegraphist s cramp, while in other occupations cramped positions of working and similar causes may help to bring on trouble in susceptible individuals

In workers who are constantly using scissors or grasping a plane or drill or other tool tightly in the hand or who have to keep exerting pressure with the leg in the course of their work or keep stretching the limb at the knee the pressure on the hand or the traction on the limb has been thought to be responsible for local changes in the muscles and nerves which produce the occupation disability These cases will be referred to again later when we come to discuss the pathology of the condition They belong to a group of pressure neuritis or occupation atrophy cases that differ somewhat in their pathogenesis and symptoms from the ordinary neurosis cases

Symptoms

In describing the symptoms of occupation neurosis it will be convenient to take writer s cramp or writer s neurosis which is the commonest and best known example of the condition as typical of the whole group and describe the symptoms first of all as they occur in it They may then be discussed very briefly as they occur in various other neuroses

Writer s Cramp

Writer s cramp usually comes on gradually in the course of long continued writing day after day although occasionally it may develop quickly or even suddenly after some short period of more or less excessive writing Various sensory and motor symptoms are present in the hand and arm in different cases and interfere with the patient s writing but for the most part the cases fall into two groups cases of writer s cramp in the strict sense and various neuralgic conditions that belong to writer s neurosis in the larger sense

In some of these severe cases the patient may try steadying his wrist and arm with his other hand and forming his letters by moving the arm as a whole from the elbow or shoulder or by keeping his elbow tightly pressed against his side and moving his body back and forth but as the spasm becomes more severe and extensive any legible writing becomes more and more difficult and impossible The spasm in any group of muscles tends to provoke as the patient tries to control it a corresponding contraction in the antagonist groups of muscles and in extreme cases with widespread tonic spasm all the muscles of the limb become so tight and rigid on the attempt to write and the movements of the hand and arm so constricted that the patient may scarcely be able to make a mark on the paper and to write a word legibly is out of the question

Many cases of ordinary writer s cramp however never reach these extreme grades and the spasm may long remain limited to the thumb and fingers holding the pen or involve only the hand and wrist In many cases too the spastic phenomena may be very slight or indefinite in character and sometimes indeed it may be difficult to say there is any actual spasm In these cases weakness in holding the pen and poorly sustained contractions in the muscles may be responsible for the slipping of the pen and the difficulty in writing or various elements of irregularity of contraction and mal coordination may enter into the condition

The tremulous and paretic varieties of writer s cramp are very much less common than the spasmodic form A certain amount of tremulousness is often present in association with the rigidity of the spastic type and com binations of tremor and spasticity are not infrequent but in the so called tremulous type the motor symptoms consist mainly of a tremor which shows itself in the act of writing but is not apparent in other uses of the hand while spastic symptoms are slight or absent The paretic form of the disability in pure form is very rare although the feeling of helplessness and exhaustion in the muscles that is characteristic of it may be present to varying extent in association with many slighter cases of the spasmodic type In the true paretic variety great fatigue and weakness come over the hand on writing so that although there is no spasm the patient is unable to move it it seems as if glued to the paper and the attempt to move it feels to the patient as if being done against great resistance In some cases this paresis is said to affect certain muscles only or more than others and in the classical example of the condition the patient could do his writing if he used his left hand to move the paper but was unable to keep his writing hand travelling across the sheet of paper on which he was writing

In most cases of ordinary writer s cramp sensory symptoms are present to greater or less extent in association with the motor phenomena and reference has been made already to the feelings of aching and fatigue that

but tending to spread, as the condition advances to various other muscles in the hand or arm In some well developed cases the spastic condition occurs in more or less pure form and the spasmodic contractions become very severe and extensive In such cases the spasm usually affects the thumb and first two fingers to begin with, although occasionally it may start in one of the other fingers or in the wrist or even in the arm It is usually a tonic contraction and most commonly involves the flexor muscles After the patient has been writing for a little time his first finger becomes strongly flexed and creeps up the pen and slips off it so that the pen gets displaced between his two first fingers He takes to using his second finger instead of the first to hold the pen but it too, may become affected in the same way or sometimes as he writes with his first finger resting on the pen his second finger keeps slipping underneath without his being able to control it or his thumb becomes flexed into his palm between his fingers and pushes the pen aside In some severe cases, a gradual uncontrollable tightening of the thumb and fingers about the pen takes place until one or other of them slides off it or the fingers become so spasmodically contracted about it that the patient can only move it to write by moving his hand as a whole Sometimes the spasm affects the extensor muscles instead of the flexor so that he has difficulty in keeping sufficient pressure on his pen to write or cannot control his fingers to hold it and it falls out of his hand In other cases again a flexor spasm occurs in one finger and an extensor in another and they become stiffly contracted in quite erratic fashion as he writes Occasionally too in addition to the tonic spasm movements of a clonic character occur in some of the muscles and the pen may be jerked out of the hand by a sudden involuntary contraction

In some severe cases the spasm may involve all the fingers and wrist or even the whole arm and shoulder When the patient tries to write his wrist and fingers bend downwards or his hand is raised off the paper or his forearm rolls persistently inwards or outwards against all his efforts to control it When his arm is involved it may be drawn tightly to his side or in other cases be violently abducted from the body and in the more extreme cases still the muscles in his neck and various parts of his body may be thrown into sudden tonic contraction on the attempt to write In a patient in whom this extensive spasm is present it may be noticed that when he tries to write his right elbow and hand are pulled tightly in towards his side and his right shoulder pushed up stiffly while his head is bent downwards to the left his left shoulder approximated to his left hip and his whole body pulled over towards the left away from his writing When the writing is stopped the muscles relax and the arm recovers almost at once In other patients other combinations of widespread tonic contraction may occur and lead to the assumption of various grotesque attitudes

have never developed to any extent and in which the condition seems to have advanced along sensory lines rather than motor

In typical cases of writer's neurosis the symptoms motor and sensory are present only with the act of writing and the patient can use his hand quite well for all other purposes and its power seems unimpaired As the disorder continues however there is a tendency for the same symptoms to occur from other actions as well as that of writing The pain of the neuralgic types is much more likely to be excited by other uses of the hand than is the spasm of the motor variety and earlier in the course of the affection but not infrequently the spasm also may be brought on by other things and especially by actions requiring similar fine movements of the fingers and hand and in this way the patient may develop multiple neuroses At first too the symptoms come on only after writing for some time then in shorter and shorter intervals and finally the mere attempt to write may be sufficient to bring them on

Telegraphist's Cramp

One of the next most common of the occupation neuroses is telegraphist's cramp The most frequent form of this as has already been mentioned is that associated with the use of the Morse key type of instrument but a cramp occurs also with the other kinds of instrument the Baudot and the Hughes The symptoms of Morse key cramp are divisible like those of writer's cramp into sensory and motor In their analysis of thirteen cases of telegraphist's cramp Thompson and Sinclair found that the sensory symptoms are usually the earlier and consist of pain aching and stiffness in the hand or arm definitely associated with the work of operating the instrument and coming on at varying times after the operator begins or even straight away The second stage of the affection which supervenes if the work is persisted in is characterized by the appearance of a visible spasm in the muscles of the hand or arm an involuntary violent and painful contraction of the muscles sometimes of the extensor muscles of the fingers sometimes of the flexors or of both and this may be associated with tremors or other motor phenomena just as in writer's cramp The operator has difficulty in manipulating the key his sending becomes slower the dots and dashes are poorly distinguished his work becomes less automatic and slower and as the condition advances it may become impossible for him to send at all In very severe cases the spasm may spread as in writer's cramp to other muscles in the limb and even lead to the adoption of grotesque attitudes by the patient in sending in which the whole body more or less becomes involved in excessive widespread muscular overaction The course of the affection is in every way parallel to that of writer's cramp

are apt to occur in the early stages of the affection The patient notices an aching and sense of fatigue in his hand or arm after writing some time or at the end of his day s work and as the condition progresses these feelings become gradully more severe and insistent and come on in shorter and shorter intervals after he begins to write Sometimes he complains of a tingling and numbness in his fingers and hand or a sense of stiffness and weakness in them or various other feelings of discomfort and even actual pain *As the disorder advances various pains may be present He may* complain of a pain shooting up from his hand to his elbow or a pain like neuralgia in his arm or shoulder or pains in his muscles and joints Occasionally in cases of extensive cramp the pain may be in his neck or in the side of his body and not infrequently in severe cases it may persist for some hours after he stops writing or come on during the night as a dull aching while sometimes points of tenderness may be found on pressure in the hand or along different nerves in the arm especially the ulnar and the median

The importance of these sensory symptoms varies very much In some *cases they may be very slight or absent throughout in other cases they* seem to develop side by side with the motor symptoms and characterize the condition to a greater or less extent In cases of more or less acute onset and rapid progress pain is apt to be a prominent symptom and severe and extensive spasms involving the arm muscles are frequently accompanied by considerable pain In the cases of slower onset and those in which the spasms long remain limited in extent pain and all other sensory symptoms are often slight and quite overshadowed by the motor disability and in some of the very slowly developing cases the motor phenomena may come on insidiously from the first and sensory symptoms be quite absent

In certain of the neuralgic varieties of writer s neurosis however motor symptoms never develop to any extent or their advent may be indefinitely postponed and in these cases the sensory symptoms of aching fatigue and pain constitute the chief or only evidence of the neurosis and are entirely responsible for the disability in writing In such cases the early feelings of *aching and fatigue become unduly prominent and obtrusive* other subjective sensations of burning tingling or numbness in the fingers occur also various pains and feelings of discomfort develop in the arm and shoulder on writing and like the pains that accompany the cramps these may persist for some time after the patient stops writing or even come on during the night after his day s work His writing becomes slower and more slovenly in character and as the condition gets worse he has to lay the pen down every little while and rest or even desist from writing altogether These neuralgic cases form a large and important group of cases of writer s neurosis in the broader sense and many of the early and slighter cases of the affection belong to this group as well as later cases in which motor symptoms

muscles of the thigh may be involved in motor symptoms and a unique case of treadler s cramp was described some years ago from the National Hospital by Dr Rivers in which the patient developed a spasm and paretic condition of the thigh muscles which showed itself especially in the upward movement of the thigh so that flexion at the hip was performed with great difficulty as if resistance were being overcome the thigh becoming inverted in the process

The muscles of the face and especially those about the eyes and the mouth are occasionally involved in occupation neuroses and one example of this may suffice by way of illustration A trombone player who had been engaged in playing a trombone for twenty seven years complained that for nine or ten months before coming to the Hospital he had suffered from pains in the back of his head and in his neck and shoulders which came on only when he was blowing his instrument and passed off when he stopped playing At the same time he had gradually developed various involuntary movements which interfered with his playing properly His lips would become drawn up so as to prevent him from playing or whenever he attempted to blow the muscles of his face and neck would go into excessive action while his tongue would keep getting in the way inside his mouth and these movements had got so bad and so beyond his control that finally it had become impossible for him to play at all

Occupation neuroses are frequently characterized by various features that bring them into close relationship with functional nervous conditions of psychasthenic neurasthenic or hysterical nature In most cases nervousness plays a part in causing or aggravating the symptoms of the neurosis the condition is apt to be worse when the patient is watched and more or less mental excitement usually attends his attempts to perform the affected movements There are some cases however in which psychical factors are entirely predominant The disability has arisen first of all under the stress of some emotion or mental disturbance connected with the patient s work or only shows itself when he is in the presence of certain persons who inspire in him fear or dislike or only when he is in certain places or when he is doing certain special parts of his work A clerk with writer s neurosis for instance may have the greatest difficulty in writing out a report for his superiors or in signing his name to it if anyone is watching him and yet at other times or in ordinary writing when he is by himself notice no difficulty at all

In many cases too various neurasthenic symptoms may be present in addition to the local occupation disability or occasionally the neurosis may develop in association with a neurasthenic breakdown and the local occupation symptoms which are usually in such cases of the sensory or slight motor type become so overlaid with various other aches and pains of a

Various Other Occupation Neuroses

It will be impossible to describe in detail the neuroses that occur in all the various occupations with which the condition is associated but in all these occupations neurosis symptoms arise similar in every way to those that occur in writing and telegraphy except that in many occupations the movements that become deranged are simpler in character Writing requires very specialized complicated movements and hence its neurosis is apt to be more complex and varied in character than that which occurs in occupations of simpler movements but in all the occupation neuroses whatever the occupation the condition is characterized by the occurrence of sensory or motor symptoms or both and these are comparable in their general character course and relationship to the occupation causing them to the symptoms that occur in writer s and telegraphist s cramp Of the two groups of symptoms sensory and motor the motor are often the more definite and clear cut in their relation to the occupation and to the particular part of the limb or body involved the sensory are apt sometimes to be less defined occur more widely over the limb and with other uses of it to a greater extent than the motor and persist more frequently after the cessation of the act causing them

Piano players may suffer from either the neuralgic or spasmodic variety of the disorder in the neuralgic variety there may be pain in the fingers or extending up the arm or even in the shoulder or back in the spasmodic variety the fingers do not move properly they remain extended so that there is a difficulty in striking the notes or they become pressed too tightly on the keys Violinists and flute players occasionally have a cramp affecting the fingers but it is rare in these occupations In violinists it is usually the hand that fingers the strings that is affected although it may be the bow hand Milker s cramp in dairy maids consists of a painful tonic spasm affecting either the extensors or flexors of the fingers and hands In seamstresses and tailors cramp there occurs a rigidity and spasm of the fingers and especially of the thumb and first finger of the right hand In blacksmith s cramp there is a tonic spasm of the upper arm muscles which is exceedingly painful as is frequently the case in the cramps involving the larger muscles

In the lower extremity the condition is much less common Various pains in the thighs of the nature of occupation neuralgia occur sometimes in patients who work a machine with the foot all day and they are sometimes very severe in character In dancer s cramp which occurs in professional dancers from the continuous contraction of the calf muscles required in standing on the toes a painful tonic spasm of these muscles may occur as the patient attempts to glide forward on the toes Occasionally the larger

ame category as that of the true occupation neuroses In addition to the wasting they may show slight sensory loss paraesthesiae pains and tenderness but they lack the spasm of the neurosis cases and the disability in the use of the muscles is a general one and not limited to the use of these muscles in special occupation movements in the way so characteristic of the typical neurosis cases The atrophy may appear however not only in occupations where the pressure of some instrument easily explains its occurrence but also occasionally in other occupations where there is no such pressure and where any difference in causation from that which produces the ordinary neurosis condition is difficult to discover There are occasionally cases too in which slight atrophy is combined with neurosis symptoms the cramps that occur in the large mu cles e pecially being sometimes accompanied by wasting in these muscles

Pathogenesis

There are no morbid anatomy changes in occupation neurosis as far as our knowl dge goes and if we except the small group of occupation atrophies the absence of the ordinary physical signs of organic nervous disease makes it unlikely that the disorder is due to any gross lesion in the nervous or muscular systems The pathogenesis of the condition therefore is obscure and mainly a matter of assumption from the character of the symptoms

The frequent association of the affection with other conditions of neurosis neurasthenia psychasthenia and hysteria and the psychical factors present so commonly in its etiology and symptoms suggest a central or cerebral origin for it in many cases Its sensory symptoms may pass into purely psychical pains and its motor symptoms into conditions of tic and the most adequate explanation of the affection in such cases is that it is a functional disorder of psychogenetic origin

In the cramp group of cases too the fact that all the ordinary movements of the affected muscles may be quite normal while only one particular and often complex movement is di turbed suggests that the condition is due in these cases to a breakdown in the central coordinating mechanism by which the action of the different muscles is associated together for the performance of the particular movements that are deranged rather than that it is a disorder of the muscles and nerves themselves In these cases the condition would seem to be an exhaustion neurosis affecting this coordinating mechanism or the result of an irritable weakness in its different parts afferent and efferent so that irregular and excessive nervous impulses sensory and motor arise whenever the particular movement is attempted

In many cases of the affection however it is probable that some of the

neurasthenic character that they are of quite secondary importance and the specific identity of the neurosis becomes blurred and indistinct

In other patients of unstable temperament the local occupation symptoms may become unduly magnified or distorted in character The sensory symptoms become persistent and exaggerated out of all proportion to their real value and a localized pain that at first sight might have seemed the pain of a sensory occupation neurosis becomes the fixed psychic pain of a purely hysterical condition In a similar way amongst the motor symptom the tonic spasm in whole or in part sometimes becomes divorced from any special exciting cause whatever and occurs more or less spontaneously, as the patient moves about or stands still and thus becomes merely an occupation tic

In these nervous patients too the affection is apt to arise with a readiness that is in marked contrast to its slow and gradual onset in other patient during long years of work day after day and not only so but it sometimes transfers itself with equal readiness to another occupation when the patient gives up his first work on its account an ease of development and readiness of transfer that frequently betoken a large element of ordinary hysteria

In various ways therefore some cases of occupation neurosis become closely related to neurasthenic and hysterical conditions It is especially in those cases in the production of which other causal factors have been prominent besides the long continued performance day after day of certain occupation movements that this relationship becomes so noticeable In these cases the affection is often very obviously merely part of a general neurosis or the manifestation of a neuropathic tendency but in the investigation of any case of occupation neurosis of whatever kind this aspect of the complaint must be borne in mind

Physical Signs

In occupation neuroses there are usually no physical signs of organic nervous disease to be associated with the condition In some cases a slight diminution of response to electrical stimulation may be present in the affected muscles in others none at all Slight quantitative electrical alterations however, are not of much importance by themselves as a sign of organic disease In a few cases too slight localized wasting is present in the muscles that are involved in the neurosis

Localized wasting is especially characteristic of a small group of conditions of occupation disability in which the pressure of an instrument would seem to be responsible for the development of neuritic changes in small terminal nerve branches Most of these cases do not belong to the

same category as that of the true occupation neuroses In addition to the wasting they may show slight sensory loss paraesthesiae pains and tenderness but they lack the spasm of the neurosis cases and the disability in the use of the muscles is a general one and not limited to the use of these muscles in special occupation movements in the way so characteristic of the typical neurosis cases The atrophy may appear however not only in occupations where the pressure of some instrument easily explains its occurrence but also occasionally in other occupations where there is no such pressure and where any difference in causation from that which produces the ordinary neurosis condition is difficult to discover There are occasionally cases too in which slight atrophy is combined with neurosis symptoms the cramps that occur in the large muscles especially being sometimes accompanied by wasting in these muscles

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In many cases of the affection however it is probable that some of the

symptoms are to be referred to a peripheral origin rather than a central In the early stages of the condition and in some of the early sensory cases that are not sharply marked off from conditions of physiological fatigue the aching and discomfort are probably merely the expression of strain and fatigue in the muscles themselves The occasional occurrence of slight wasting too in the muscles involved in the neurosis suggests the influence of a peripheral factor in the pathogenesis of the condition This wasting occurs for the most part in the small group of cases that has been referred to as the occupation atrophies but it may occur in occupation neurosis itself and the two groups of conditions are closely associated in many ways

In most of the occupation atrophy cases the wasting is probably due to pressure neuritis involving the finer nerve terminals or sometimes even the larger nerves Occasionally however there are cases of atrophy in which the supposition of a pressure neuritis as a cause is not so easy and in these cases the explanation of the wasting is more difficult The prolonged muscle contractions however may produce in such cases a condition analogous to that which occurs from prolonged tetanizing of a muscle by the faradic current the renewal of the blood supply and the removal of waste metabolic products being interfered with by the continuous contraction and the nutrition of the muscle consequently damaged It is possible too that the long continued repeated contractions and the constant movements of joints and limbs and especially the repeated movements at the larger joints may cause tension traction or pressure on nerves or nerve terminals and that in such ways local injury to the nerves or the muscles may result from normal functioning indefinitely repeated

As the occupation atrophy condition and the true occupation neurosis both occur in the same and similar occupations these arguments for a peripheral pathology would seem equally applicable to the neurosis cases and it is not unlikely indeed that finer peripheral, pathological changes may be present in some cases of true occupation neurosis but, although local neuritic or myositic changes may be associated with the development of the neurosis condition its progressive and characteristic spread and distinctive features in typical fully developed cases would seem to demand a psychogenetic factor as well as the essential part of its pathogenesis

Prognosis

An occupation neurosis usually runs a very protracted course and if the *occupation movements at fault are persisted in the disability tends* to get steadily worse and the symptoms may gradually become so severe as to render the work impossible The rate of progress varies very much however

in different individuals In many typical cases associated with the long continued performance of occupation movements it is very slow In cases where accessory nervous causes are prominent it is apt to be more rapid

The prognosis in any individual case depends therefore on the length of time the condition has been in existence before the patient seeks advice or treatment the extent character and severity of the symptoms present the mental and nervous temperament of the patient and the degree to which anxiety and worry are present in cases where his means of livelihood are interfered with by the neurosis

Many slight cases in which sensory symptoms only are present recover entirely but for the most part slowly In the spasmodic variety of the affection recovery may take place also but where the spasm is well established and fixed the hope of sufficient recovery to enable the patient to carry out the affected movements with normal facility is not good and if the *neurosis has developed during a long period of excessive work day after day* and there is extensive visible spasm the outlook for recovery is very bad In those cases in the production of which various accessory causes have been active besides the long continued excessive performance of the occupation movements and especially those in the production of which nervous and mental causes have been active the immediate outlook is more variable In many of these cases the time taken in the production of the neurosis has been comparatively short owing to the poor resistant power of the patient and the disability is chiefly of the sensory type In such cases the affection probably depends on a less fixed pathological cerebral condition and may be expected to be amenable to the influence of treatment and rest In some of these cases too the local occupation symptoms are to some extent subsidiary to other more general neurosis features and may yield entirely to the treatment of the more general condition In many other cases however in which nervous causes are prominent the occupation disability progresses very fast motor and sensory symptoms soon become severe and extensive and in these the prognosis is very bad while in all cases in which nervous factors are conspicuous it must not be forgotten that the affection shares in the uncertainty of prognosis attendant on the unstable nervous temperament of the patient

Diagnosis

In typical cases of occupation neurosis the diagnosis would seem a very simple matter and the specific relationship of cause and effect that obtains between the occupation and the characteristic sensory and motor symptoms of the affection sufficient guide In many of the early and slighter cases however in which sensory symptoms only are present considerable

care is required in separating the affection from conditions of mere physiological fatigue on the one hand and conditions of neurasthenia and hysteria on the other Fatigue enters so largely into the initial symptoms of the neurosis that it may easily be taken for the whole condition while neurasthenia and hysteria are so closely related to some varieties of the affection that no sharp distinction between them and occupation neurosis is always possible Many of the early sensory cases moreover are somewhat indefinite in the character of their symptoms the causal relationship of some special occupation is not always strictly maintained, the pain is wide in its distribution or does not cease after the cessation of the act causing it so that in the estimation of these cases doubt frequently arises and considerable reliance in the diagnosis has to be placed on the general aspect of the case as a whole

When motor symptoms are present to any extent the condition is a much more definite one and the diagnosis usually becomes easy the specific relationship of the spasm to the occupation and the normal utility of the muscles for ordinary uses leave very little room for doubt Sometimes in these cases other local functional conditions such as tics and hysterical tremors have to be excluded as they too may cause a disability in the carrying out of various occupation movements but this is easily done apart from any differences in the character of these affections themselves by the absence in them of this specific relationship to the occupation A patient for instance with a shrugging tic of the arm or shoulder may have an involuntary jerking movement in his writing owing to it, but no sign whatever of writer s cramp

Before diagnosing any case of occupation neurosis however it is always necessary to examine the patient very carefully for any signs of organic disease of the nervous system Many organic diseases in their early stages interfere considerably with the performance of fine manipulative movements and thus may simulate the disability of an occupation neurosis In the hands for example a slight hemiplegia or a progressive hemiplegia coming on slowly and gradually or a condition of sensory hemiplegia or monoplegia from cerebral lesion may interfere with writing or an early progressive muscular atrophy may lead to weakness in the hand or a condition of paralysis agitans or a midbrain lesion cause a tremor in its movements Various other affections also such as tabes dorsalis or disseminated sclerosis may cause a difficulty in the coordination of the movements of the muscles and limbs Those neurosis cases too in which slight wasting is present, require to be diagnosed carefully from the early wasting conditions of organic disease of the lower motor neuron

Sometimes local conditions in the limbs such as peripheral neuritis rheumatoid arthritis weakness resulting from an old injury or old condition

of slight paralysis due to poliomyelitis have to be taken into account in the diagnosis and it is very important to appraise properly the fatigue and weakness due to these local defects before deciding on a condition of associated occupation neurosis

Treatment

The most important factor in the treatment of occupation neuroses is complete rest from the occupation or the particular part of it that is responsible for the development of the condition and the earlier in the course of the affection this is undertaken the better is the chance of recovery It is difficult however to make any general estimate of the length of time for which the rest should be advised It will vary very much according to the type of case the severity of the symptoms when the patient comes under observation and the length of time the condition has been in existence but probably in every case it should be measured in months rather than in weeks and in severe cases it may have to be laid down from the beginning as quite indefinite

In some advanced cases where the prognosis is obviously very bad when the patient comes under observation and it is quite impossible to forecast any likelihood of his being able to resume his work after a reasonable interval the question has to be considered whether he ought not to alter his occupation permanently and there are advantages sometimes in deciding this at the outset without making tentative efforts at treatment especially if the patient is young and a change of occupation can be readily made

In early or even moderately advanced cases however it often happens that the patient is unwilling or unable to rest from his work entirely Questions of livelihood have to be considered and in order to prevent the worry and anxiety to him that would otherwise ensue a compromise is frequently adopted and he continues doing his work with some modification or rearrangement of it or shortening of his hours No rearrangement however that keeps him still doing the particular action that has caused his neurosis can be regarded as satisfactory or ideal all other measures in his treatment are vitiated by it his condition usually progresses and the disability becomes more and more confirmed and less likely to respond to rest when at length this is forced upon him

In writer s cramp which as the most frequent of the occupation neuroses has had most attention paid to it various mechanical devices have been employed from time to time to enable the patient to continue writing such as the use of special pens with springs to counteract the spasm or with a large round ball attached to the holder which the patient can grasp in the

palm of his hand While undoubtedly in writing all errors of technique should be corrected and the patient instructed to write in a free way with large muscle movements and to use a larger penholder which is easier to hold lightly than a small one, these other palliatives are not very advisable and in any case they soon lose their efficacy

There are certain other ways however in which the patient may continue his work in the case of some occupations and yet rest the muscles affected in his neurosis In unilateral disabilities such as writer s cramp or telegraphist s cramp he may learn to use the other hand and get along in this way fairly well for years Patients who have writer s cramp too may take to the use of a typewriter in the case of some writing occupations although unfortunately not in all

Telegraphists too as well as using the other hand may sometimes use a different style of instrument such as the Baudot or Hughes instrument instead of the Morse key type In a telegraph office it is often possible also for a patient to do sorting or writing work and little or no sending Musicians too may keep on with the teaching part of their work while giving up their own playing in public and long hours of practicing In most occupations some rearrangement of work is often possible in ways like these and this may meet the case to some extent where a complete rest is impossible

Apart from the cessation of the work the other measures to be adopted in the treatment depend very much on the character of the individual case and the associated conditions that are present The patient s general health may be benefited by tonic treatment and by a short stay in congenial surroundings in the country and in many cases this is a very advisable procedure at the outset of treatment Sometimes for patients who can afford it travel and change of scene may be advised if the neurosis is a very severe one Clerks in shipping offices who develop writer s cramp for instance have sometimes derived great benefit from a long voyage in which they are given some light work to do or some responsibility in connection with the voyage

In patients in whom neurasthenic symptoms are prominent the ordinary treatment for neurasthenia is applicable and massage and stimulating electrical treatment may be employed in addition to more or less complete rest In such cases the massage and electrical treatment should not be limited to the affected arm or limb Some form of neurasthenic treatment too in which the patient is given light occupation to keep him employed is usually better than any prolonged use of that requiring rest in bed methods for mere idleness is usually bad for the neurosis condition

Apart from their value in the treatment of the associated neurasthenic or hysterical symptoms massage and electrical treatment of different

kinds and various exercises locally to the affected limb are not of great value in themselves in the treatment of the disability and they probably act only by their general stimulating effect and their psychical effect as suggestive agents

For those patients whose neurosis is associated with prominent psychical symptoms psychotherapeutic treatment may be advocated This is likely to be of most benefit in cases in which the local neurosis is the outward manifestation of some psychical disturbance or some special fear or complex is associated with its onset In such cases the investigation of this by careful inquiry may result in the cure of the disability These cases however are of a special type of the affection and very different from the slowly developing cramp variety

If the patient seems to be improving after a reasonable rest he may resume his work In doing so certain general precautions should be adopted he should begin the work again gradually and increase the daily amount he does very slowly If possible the work should be varied so that no long time is spent continuously on the particular part of it that was at fault and various expedients such as have already been outlined may be made use of in order to relieve him to some extent of this part of the work and make his resumption of it gradual and tentative

If the result of the attempt to resume his work is disappointing as it often is in cases in which treatment has been begun late the patient will have to rest from it further or consider the question of making arrangement permanently to limit the particular part of it at fault or to change his occupation entirely

CHAPTER XXXVIII A

ALCOHOLIC INTOXICATION AND ALCOHOLISM

By EDWARD A. STRECKER AND THURSTON D. RIVERS

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In recent years the study of the effect of ethyl alcohol on the human system has received tremendous impetus. However as Newman observes the points upon which authorities have come to complete agreement are relatively few. It is germane to the purpose of this chapter to discuss at some length the controversial status of much of our knowledge. We shall endeavor to cover the broader aspects of the role of ethyl alcohol

its absorption distribution oxidation and action upon the human organism

Absorption of Alcohol

Alcohols may be absorbed into the body by oral ingestion by subcutaneous injection by intraperitoneal injection through inspired air by intravenous injection and by proctoclysis Clinically absorption by the oral route alone is of interest Alcohol is one of the substances absorbed in appreciable amounts through the gastric mucosa It is however in the small intestine that by far the greater and more rapid absorption takes place Several factors naturally influence its absorption There is an optimum concentration of alcohol for absorption from 10 to 20 per cent being absorbed more quickly than are higher or lower concentrations It is well known that food has a marked effect upon the absorption of alcohol Mellenby found that the administration of milk before alcohol had a marked effect upon both the rate of elevation and the maximum concentration of blood alcohol in dogs Emotional states because of their effect upon gastric emptying time and changes in the autonomic tonus of the gastrointestinal tract may influence the absorption time Surprisingly enough habituation has been shown not only to slow the rate of absorption but to some extent to inhibit it With these variables in mind it is not surprising that the actual rate of absorption is difficult to ascertain Newman states that 90 per cent of a moderate dose of diluted alcohol taken on an empty stomach is absorbed within an hour

Distribution of Alcohol in Body

Alcohol concentrations throughout the body are dependent upon the water content of various organs i e those having a higher water content contain more alcohol

Oxidation of Alcohol

Bearing in mind that only 10 per cent of injected alcohol is excreted by the kidneys lungs and sweat glands it follows that the remaining 90 per cent must be oxidized in the body a fact of considerable importance in view of the controversy over the food value of alcohol Only recently the site of this oxidation has been localized in the liver but knowledge of this process still is incomplete Since each gram of alcohol is equivalent to seven calories one pint of 90 per cent alcohol would make available

1 190 calories a not inconsiderable portion of the daily caloric requirements of a man if this were made available as energy Though the mass of evidence is somewhat confusing it would appear that little if any of this alcoholic caloric intake is available for muscular energy Alcohol may act to some extent to spare carbohydrates but it is unable to replace carbohydrates as has been shown by its inability to relieve hypoglycemic shock when given by mouth or vein Indeed there is some evidence which demonstrates that glycogen stored in the liver and muscles is mobilized and reduced to glucose to accomplish the oxidation of alcohol

Action of Alcohol upon the Human Organism

The direct toxic effect of alcohol is most marked on the central nervous system There is a universal agreement supported by psychological tests that the effect of alcohol on the central nervous system is one of *depression and later paralysis of function The method by which this* depression takes place is not clear but the similarity between the symptoms of acute alcoholism and anoxia is quite suggestive McFarland and Barach have been able to increase the performance of 75 per cent of a group of 23 who had been given large doses of alcohol by placing them subsequently in an atmosphere of high oxygen concentration

Death from acute alcoholic toxicity occurs infrequently and when it does occur is caused by a high alcohol concentration in the respiratory center Newman feels that any blood alcohol concentrations above 0 5 per cent may result in death

Gastrointestinal Complications

The effect of alcohol upon the alimentary tract has been investigated extensively and more is known concerning its physiological action than concerning its clinical picture Alcohol in any concentration causes an increase in the flow of saliva this is by direct stimulation of the nerve endings in the tongue and buccal mucosa and not as in the case of the stomach due to alcohol concentration in the circulating blood The enzymes in the saliva are fairly resistant to the action of alcohol however in concentrations of 10 per cent or over ptyalin is rendered inactive A glossitis and stomatitis in a large group of alcoholics has been described by Blankenhorn and Spies Although it responds well to the administration of vitamin B_1 and nicotinic acid these authors are *unwilling* to ascribe it entirely either to alcohol or a vitamin deficiency disease It may possibly result from a combination of the two

The prolonged consumption of large amounts of straight whiskey may produce an acute esophagitis with spasm This spasm is more apt to occur at the esophageal gastric junction The evidence pointing to alcohol as a chronic irritant and consequently an etiological factor in cancer of the esophagus must be questioned as inconclusive The fact that a large percentage of patients suffering with esophageal cancer use alcohol habitually cannot be accepted as proof of its etiological responsibility

The changed secretion of gastric juice following the administration of alcohol has long been recognized clinically and generally This latter fact may be responsible for the widespread antecibal use as a carminative Alcohol has a dual effect upon the gastric secretion first it increases the secretion of acid and second it acts as an irritant in concentrations of greater than 15 per cent and promotes the secretion of a juice rich in mucus In high concentrations it exerts an inhibitor effect There is some reason to believe that the secretory stimulating effect of alcohol upon the gastric mucosa may be due to its ability to liberate histamine The habitual use of alcohol indubitably can produce an acute gastritis Much evidence exists corroborating the production of this inflammatory reaction Insofar as the production of a chronic gastritis is concerned the association is not so clearly established The difficulty in establishing its etiological relationship seems in part at least to be dependent upon the associated vitamin deficiencies seen in the habitual users of alcohol Schindler from a gastroscopic analysis feels that the prolonged use of alcohol seems to produce chronic gastritis in some patients while in others it has no effect The question of an associated nutritional deficiency likewise has been studied carefully and there is some reason to believe that the defect is attributable to a deficiency of some component of the vitamin B complex

The role of alcohol in the production of peptic ulcer is related to the questionable etiology of chronic gastritis in the production of ulcer Standard medical practice contraindicates the use of alcohol in the presence of either Large quantities of alcohol in concentrations of from 5 to 10 per cent inhibit hunger contractions and the action of digestive enzymes and depress certain liver functions Pancreatic juice secretion is slightly increased

Effects of Alcohol on the Liver

The effect of alcohol on liver function and the ultimate production of cirrhosis of the liver indicates that alcohol facilitates but is not imme

diately responsible for its development Conner and Chaikoff reason that on the basis of the production of a fatty liver alcoholic cirrhosis may ensue Moon in his review of the literature up to 1934 concludes that up to that time cirrhosis had never been produced by alcohol alone in any animal other than the rabbit Mallory also feels that alcohol can be ruled out as a cause of portal cirrhosis In all successful experimental work on animals chemicals toxins trauma insufficient or faulty diet or marked vitamin deficiency have been used in conjunction with alcohol to produce cirrhosis However it would be erroneous to assume that alcohol can be exonerated entirely as a factor in the production of portal cirrhosis There is a mass of clinical evidence to indict alcohol in this respect From a survey of the present status of the etiology of portal cirrhosis we are safe in assuming the view that while alcohol per se can be and frequently is a contributing factor in the production of cirrhosis it is not alone directly responsible

Alcohol and Nutritional Deficiencies

The newer concepts of nutritional deficiencies nowhere have been demonstrated more clearly than in the complications and sequelæ of chronic alcoholism As Jolliffe has explained The factors furnished by alcohol which increased the prevalence of nutritional deficiency diseases in addicts are primarily four (1) the irritant action on the gastric mucosa (2) the interference with absorption and utilization of the vitamins (3) the substitution of vitamin free alcohol for vitamin containing food (4) the increased vitamin requirement in consequence of the calories furnished by the alcohol

Neurological Complications

Alcoholic neuropathy is a complication of alcoholism occurring in 15 to 20 per cent of the more chronic alcoholics It evidences itself by symptoms of neuresthenia insomnia and fatigue cramps of the calf muscles burning of the soles of the feet and palms of the hands accompanied by paræsthesias of the toes and fingers Later calf muscle tenderness appears which can be elicited by squeezing Hyperesthesia of the soles of the feet is marked The neurological signs at this stage are absence of ankle jerks and diminished or absent vibratory sensation in the toes The signs remain limited to the lower extremities until the disease becomes quite advanced when the upper extremities become involved and the biceps and triceps jerks disappear Dysesthesia of the sole of

the foot and palm of the hand are among the most annoying symptoms In its most advanced stage there is a foot and wrist drop and atrophy of the calf muscles No matter at what stage the neuropathy is observed always it is symmetrical and bilateral Cardiac complications such as dyspnea palpitation and tachycardia are manifested during the course of the process

The use of the name alcoholic neuropathy is a misnomer Today practically all investigators agree that it deals with a nutritional deficiency quite similar in its morbid pathology to beri beri Jolliffe believes that it is purely a thiamin chloride deficiency and that it can be cured by an adequate dosage of this vitamin Meiklejohn and others accept the fact that it is a vitamin deficiency but feel that the deficiency is multiple rather than of vitamin B_1 alone More work must be done in order to establish firmly the exact etiology Adequate diet supplemented with large doses of the vitamin B complex is at present the treatment of choice

Wernicke s disease called by Wernicke *polioencephalitis hemorrhagica superior et inferior* is a response to alcohol differing from Korsakoff s psychosis only in its severity and the distribution of the lesions This disease is characterized pathologically by small petechial hemorrhages with degeneration and necrosis of the parenchyma Gliosis with underlying proliferative vascular changes completes the pathological picture Bender and Schilder divide the cases into five groups on the basis of clinical findings (1) cases with the classical picture of polioencephalitis hemorrhagica superior with clouding of consciousness (2) those in which cerebellar disturbances are more prominent (3) those resembling acute catatonia in mental and neurological features (4) cases in which the delirious symptoms are more marked than the neurological ones (5) those in which the polyneuritic features are associated with various polioencephalitic signs Alexander and other workers by creating vitamin B_1 deficiency have been able to produce experimentally in animals pathological lesions which are identical with those of Wernicke s disease in man The fact that Wernicke s disease is found without the complicating factor of alcoholism leaves little doubt that one is dealing here with another condition in which the etiological factor of alcohol need be considered only insofar as it contributes to the vitamin deficiency

Psychiatric Complications

The excessive use of alcohol causes a profound disturbance in the organization of the personality of an individual This has led to the popular conception that a long continued use of alcohol with frequent disruptions of the personality would produce in time a permanent de

rangement However the present view among psychiatrists is that alcoholism does not occur in a normal personality but is a symptom rather than an etiological factor Bowman states that in many cases the use of alcohol is symptomatic of an underlying mental disorder Knight feels that no excessive drinker is normal and well adjusted even when he is sober and that in alcohol addiction there are always neurotic trends or paranoid or schizoid features Strecker and Ebaugh have the opinion that alcoholism may be a symptom of other psychoses but in itself accounts for from 5 to 10 per cent of all mental disease Minski goes so far as to state that alcoholics are not actually suffering from a particular form of mental disorder resulting from alcohol but they present the same symptoms for which other patients are admitted

If we except delirium tremens and Korsakoff s psychosis alcohol might be considered to be the precipitating factor in a previously existing pathological process This concept does not include the complication of alcoholism in a frank psychosis such as might occur in the depression of a manic depressed in general paresis or in frank schizophrenia

The diagnosis of a so called alcoholic psychosis is important from the standpoint of treatment and prognosis While the various classifications may differ in their subdivisions in their wider scope they are quite similar In a recent article Bowman and Jellinek have given a comprehensive classification which is simple and satisfactory

Acute Alcoholic Intoxication

While temporary and self limited in its duration the behavior and disturbance of personality pattern in acute alcoholic intoxication is such that it must be considered as a toxic manifestation of alcohol per se Probably more truly than any of the other alcoholic states it is a direct result of and dependent upon the alcohol consumed and is as in most toxic states the reaction of the pharmacological action of a toxic agent upon the personality of the patient The picture runs the gamut from hilarity to euphoria faulty judgment impaired performance to actual coma Bogen has shown that the consumption of alcohol in amounts sufficient to bring its concentration in the urine to 4 or 5 milligrams per c c will result in narcosis and stupor There is usually no amnesia for the period of intoxication

Pathological Alcoholic Intoxication

This differs from the above acute alcoholic reaction quantitatively rather than qualitatively In this type of reaction motor incoordination

slurring of speech and diplopia usually are absent amnesia for the period of intoxication frequently is present It is characterized by blind rage and confusion and may last from a few minutes to several hours The chief neurological manifestation is a loss of pupillary reflex It is in this type of alcoholism that the role of hypoglycemia recently has been emphasized It occurs most predominantly in psychopathic personalities who Bowman observes even in the absence of drinking show unprovoked fits of rage It may also occur in people who have had previous brain injury Alcohol in these instances acts merely as an inciting agent in setting off the hair trigger adjustment characteristic of those socially maladjusted In those who have central nervous system pathology release of cortical inhibition can be accomplished similarly by many other narcotics

Delirium Tremens

This is probably the most familiar of all the alcoholic psychoses and because of its familiarity many other types of alcoholic psychoses frequently are placed at its door Bowman and Jellinek feel that its incidence among chronic alcoholics with or without psychosis is from 4 to 5 per cent

Prodromal symptoms may occur days or weeks before the onset of the actual delirium evidencing themselves as anxiety restlessness fear insomnia and occasional hallucinations Most of these symptoms occur as does the onset at night The classical picture of visual and auditory hallucinations is accompanied by clouding of consciousness disorientation as to time place and person hyperactivity and excitability The visual hallucinations are by far the more frequent and usually include animal of which dogs insects and snakes were reported by Dynes to be the most frequent The hallucinations both visual and auditory when present are of a threatening nature and inspire in the patient a sense of fear Kraeplin pointed out that despite the fear of which they may complain the patients seem to realize that there is a certain unreality about their hallucinations and even to retain some of their own sense of humor There are present among the most prominent physical signs a coarse tremor of the extremities muscles of the face and whole body Insomnia which is very difficult to control is another prominent sign There is a distinct rise of the blood pressure The pulse rate may increase to 125 beats per minute Probably in delirium tremens more than in all other alcoholic psychoses alcohol has been demonstrated most clearly to be the precipitating factor inducing a chain of metabolic sequelæ It is a di

case occurring in the abnormal drinker of a number of years standing Bowman and Jellinek feel that it is a psychosis of episodic nature which does not reach down to the personality structure They prefer to view it as an encephalopathy which is encountered in only a fraction of a per centage of alcoholics They feel that it is found most frequently in patients in whom there are metabolic disturbances with lo s of the detoxi fying function of the liver and consequently faulty carbohydrate me taboli m disturbed protein metabolism and dysfunction of the water economy of the body

Death occurring in these cases is due to cardiac failure since this organ usually is affected in a manner closely resembling the cardiac pathology of vitamin B_1 deficiency states The mortality has been vari ously reported 24 per cent to 0 88 per cent The theory that the im mediate withdrawal of alcohol precipitated delirium tremens in chronic alcoholics no longer is generally held Bowman Wortis and Kestler as well as Piker feel that abstinence has nothing to do with the onset of delirium tremens Noyes feels that the cessation of drinking may be indicative of an oncoming delirium While the presence of cerebral edema is recognized generally by authorities in most cases of delirium tremens active treatment by lumbar puncture has been discontinued Indeed Bowman Wortis and Kestler emphasized the importance of hydration by means of normal sodium chloride solution parenterally The cellular dysfunction would seem to result from the existence of intra cellular edema producing a swollen tight brain Such being the case the use of concentrated solutions parenterally lyophilized plasma polysaccha rides are more specific aids than is the removal of a cell transudate cerebrospinal fluid Both Piker and Bowman feel that psychotherapy accomplishes more in this form of alcohol psychosis than in any other

Korsakoff's Pyschosis

This is a relatively infrequent complication of chronic alcoholism Be cause of its interesting clinical picture and definite pathological entity it has aroused considerable interest Its onset may be either sudden in the form of delirium or slow with a marked memory disturbance loss of memory for recent events disorientation as to time place and person confabulation and it may be associated with a polyneuritis Henderson and Gillespie emphasize the symptom of confabulation which frequently demonstrates also the patient s memory defect since he repeats often the same fantastic story with slight variations This form of psychosis while toxic in origin is not always due to alcohol since it is also seen in lead

poisoning certain poisonings of bacterial origin and in the toxic vomiting of pregnancy *Jolliffe points out that the alcoholic form practically always* is associated with some degree of polyneuropathy Its association with polyneuropathy has led to its identification with a vitamin deficiency Certainly most of the patients presenting this syndrome have an associated vitamin deficiency which may be etiological Wortis and Jolliffe have shown that while the administration of vitamin B_1 may improve the neuropathy it does not influence the mental symptoms These psychoses are usually of long duration remission in less than six weeks is rare and frequently there are residual memory defects for longer periods The mortality rate is from 25 to 50 per cent Bowman and Jellinek quote Radu to the effect that the prognosis in young people is much more grave than in those of the older age group

Acute Alcoholic Hallucinosis

Alcoholic hallucinations unlike the above psychoses cannot be entirely dissociated from an underlying schizophrenic process This is emphasized by the fact that the age at onset is lower in this psychosis than in any other alcoholic psychosis It is less dependent upon a history of prolonged alcoholic consumption than other alcoholic psychoses Patients suffering from alcoholic hallucinosis show a higher incidence of psychotic antecedents than do those of Korsakoff s psychosis or delirium tremens or the population in general It is usually felt however that there is an acute hallucinosis attributable to alcohol but that by far the greater number diagnosed as such should fall into the classification of schizophrenia of which alcoholism is merely a symptom The onset of the disease when sudden is characterized by a marked fear auditory hallucinations anxiety and unimpaired orientation as to time and place Fear of impending doom contributes considerably to the picture of anxiety and suicidal attempts are not at all infrequent Visual hallucinations are not preponderant and the auditory hallucinations frequently are bizarre One of our patients for example complained that his red blood corpuscles were demanding alcohol making threatening statements and accusations Alcoholic hallucinosis differs from delirium tremens in that patients of the first type usually are well oriented and rather accessible although they do not respond to suggestion so well as the delirium tremens group The hallucinations as remarked usually are auditory rather than visual Tremor and motor activity are not so marked as in delirium tremens These combined with the difference in personality factors make the diagnosis relatively easy No statistics on the incidence

of this disease would seem to be valid because of the confusion in the diagnosis

Alcoholic Paranoid Condition

Frequently in chronic alcoholics there is seen an increased tendency towards suspicion and distrust arising chiefly while they are under the influence of alcohol but gradually becoming present at all times This may develop after years of drinking into actual paranoid delusions about infidelity of the mate domestic irritability and suspicion and ideas of persecution Nolan Lewis feels that these conditions develop on a background of a paranoid personality with lifelong peculiarities He feels that the prognosis is poor but that remissions are seen occasionally Bowman calls attention to the disorientation which may accompany this condition

Chronic Alcoholic Deterioration

Under this are grouped those conditions which arise from excessive drinking over a long continued period of time Bowman calls attention to the fact that these can hardly be called a clinical psychiatric entity per se since the manifestations are not distinct and are on the level of conduct rather than of symbolic functions He feels that while it may not be an actual psychosis it is definitely a matter for psychiatric consideration

The clinical picture is dependent to a large extent upon the cultural background of the individual Under ordinary circumstances he may be able to behave in an appropriate manner but there may be definite periods during which he shows brutality and marked dulling of the finer sentiments He is apt to be impulsive and very labile in his emotions A number of cases have been observed in which there was a history of trauma during a debauch subsequently there were abnormal electroencephalographic tracings and despite an excellent social scholastic and achievement history the psychometric examination showed definite impairment These patients showed marked loss of will power an inability to cooperate in therapy and a tendency to fabrication They were euphoric in their general attitude and showed a decided lack of affect concerning the seriousness of their condition In view of the fact that trauma is not an infrequent occurrence in the course of alcoholic debauches the question is raised as to how many of these alcoholic deteriorations are complicated by the sequelæ

Treatment of Alcoholism and of Resultant Toxic States

The medical treatment of alcoholism as well as the toxic states resulting therefrom depends upon three factors (1) supportive treatment for the patient (2) control of the symptoms and (3) the elimination of the toxic agent The patient particularly the chronic alcoholic suffering from neurological and psychiatrical sequelæ requires considerable support Obviously a patient in this debilitated state is an easy prey to any of the intercurrent infections and these must be treated specifically In delirium tremens cardiac complication is the most frequent cause of death and many practitioners in severe cases of delirium tremens administer digitalis routinely Bowman emphasizes the disturbance in water metabolism and the subsequent acid base imbalance For this he recommends the administration of sodium chloride and fluids in large amounts either parenterally or by alimentary tract Carbohydrates in the form of orange juice with sugar as well as a high carbohydrate diet also should be given freely The diet should be rich in vitamins and in addition to this the vitamin B complex should be given in high dosage We have used routinely thiamin chloride parenterally in dosage of 100 mgm daily and in addition large doses of nicotinic acid The associated gastroduodenitis often precludes the toleration and absorption of an adequate dietary and supplementary medication The parenteral use of liver extract facilitates this absorption

Most alcoholics present a peculiar problem attributable to their disturbed mental condition As regards their management most sedatives add to the already distressing picture Even when the alcohol has disappeared from the system the toxic symptoms produced by sedation may require treatment Although it is not necessary because of the physical condition of the patient to continue the administration of alcohol in the so called tapering off process and although it increases the duration of the convalescence it may be expedient to allow a much diminished intake of alcohol for one or two days This is particularly true if psychiatric treatment of the patient for his habit is to be undertaken since the physician s rapport may be more firmly established For many years the sedative of choice has been paraldehyde in doses of 1ʒ to 3ʒ to which the chief objections are its unpleasant taste and odor It is superior to any of the barbiturates not only because its dosage can be controlled more easily but also because it is excreted by the lungs and not the liver and kidneys and it is less toxic Dille and Ahlquist have demonstrated that instead of antagonism between alcohol and the barbiturates there was a marked synergism so far as the narcotic effect was concerned Benzed

mine sulphate has been used extensively both in acute and chronic states of alcoholism There is little doubt that it may be effective in hastening the sobering up process and give the patient a sense of well being However it is not without danger We have seen six cases of benzedrine psychosis following the associated use of the drug in this manner At best none of the agents above mentioned are any more than palliative and even their most judicious use will only gain time for nature to eliminate the toxic agent from the system A physiological therapy directed towards the elimination of the toxic agent with as few side effects as possible which will control also the symptoms of the patient is obviously of a distinct advantage

The original rationale for the assumption that the carbohydrate processes are involved in the oxidation of alcohol lay in the inferential conclusion that since alcohol is an intermediary product of carbohydrate combustion insulin bringing about combustion of other intermediate carbohydrate metabolic products should be effective in completing the breakdown of alcohol in vivo This has led to much speculation and experimentation with most of the evidence to date refuting this assertion

A summary of the contraversial status of these concepts seems to indicate that The liver is primarily responsible for the combustion of alcohol since it has been shown that there is a persistent high blood alcohol present in hepatectomized animals and in those showing liver damage from a variety of causes Likewise other experimental evidence as from hind limb preparations and muscular activity indicates that the muscles themselves are unable to burn alcohol directly States of liver glycogen depletion lipemias cirrhosis untreated diabetes starvation and vitamin deficiencies are inversely proportional to the rate of alcohol elimination Seckel has shown that insulin without extraneous glucose decreases liver glycogen Widmark Dell aqua Lang and von Schlick Flemming and Reynolds and others found that insulin alone produced little effect upon blood alcohol levels However Clark and associates Lundsgaard Dontcheff Schlichting Dell aqua LeBreton have shown experimentally that insulin in the presence of adequate glucose expedites the lowering of the blood alcohol levels The use of thiamin chloride provided the necessary catalyst for the intermediary carbohydrate combustion Clark Morrissey Fazekas and Welch used experimentally sodium bicarbonate and sodium citrate in a similar catalytic manner

Robinson in 1937 reported on the successful use of insulin in nine cases of alcoholic psychosis In 1939 Goldfarb Bowman and Parker described their experiments with glucose intravenously and insulin subcutaneously in the treatment of acute alcoholism Strecker and Rivers

differed in their procedure from these in that they injected the entire solution of insulin glucose and thiamin chloride intravenously The addition of thiamin chloride has a distinct advantage and the intravenous use of this combination makes it ideal for the control of an emergency situation Sedation can almost always be dispensed with even in the most disturbed patient The technique was reported as follows 100 c c of 50 per cent glucose solution 30 units of insulin and 120 mgm of thiamin chloride were placed in two 50 c c sterile syringes A twenty gauge needle was used to inject this intravenously One quart of orange juice fortified with about two ounces of cane sugar was given the patient to drink The treatment was repeated if necessary every three hours Insulin shock as has been shown is not desirable and where symptoms of it have appeared they have been combatted with additional glucose by vein

They report that in a group of over 200 patients they found this treatment efficacious in psychiatric complications of alcohol including acute alcoholism alcoholic hallucinosis and delirium tremens They also report its use in toxic conditions with an etiology arising from chloral amphetamine sulphate sulphdiazene and barbituric acid derivatives It is probable that this therapy also will prove an efficacious emergency measure for the psychiatric complications due to any toxic agent the elimination of which is dependent upon metabolism by the liver

Chronic Alcoholism

The history of alcohol is coextensive with the history of the human race The deciphering of tablets of great antiquity indicates that the Egyptians and other ancient peoples enjoyed beer Rome was drunk not only on its victories but also on its wines From cereals and honey the barbarians from the North brewed a delectable beverage called mead The Caledonians no doubt seeking to offset the bone penetrating chill from the fogs that hung over the moors produced the now highly prized Scotch whiskey Before his white brother bartered with him beads and firewater for his hunting grounds the North American Indian concocted an evil and potent beverage from gall from freshly killed elk and buffalo mixed with ashes and exposed to the heat of the sun

Anything which persists through the ages surviving legislative and other efforts to eradicate it is motivated by a powerful driving force The reason that the use of alcohol by human beings has persisted is because of the quality it has of rosily blurring the hard unpleasant and forbidding outlines of reality and if taken in sufficient quantities it has

the power of effacing reality altogether It is phantasy in a bottle Add to this the fact that it is readily obtainable produces its effect quickly and at least for a long time escapes social stigma then one may understand why alcoholism is such a tremendous economic social ethical and medical problem

Alcohol is always a narcotic and its reputation as a stimulant rests on the inhibitory release which it promotes Helpful parallels may be found in pathology of the frontal lobes or in the behavior following in the wake of extensive frontal lobe surgery and in the phenomena of the manic phases of manic depressive psychosis In these situations as in alcoholism there is loss of inhibition abolition of self critique and in general regressive behavior

Even in a social gathering which is only comparatively mildly alcoholic one may observe readily the regressive behavior so quickly achieved through alcohol Portly middle aged dowagers and gentlemen even older showing some of the infirmities of their years from their conduct obviously are re enacting albeit not very convincingly occurrences from that remote day when respectively they were beautiful and slim debutantes and gallant young bucks

Frequently in other situations complete shedding of all adult responsibility may be observed so that the drunkard becomes as helpless as an infant with profound loss of control even involving the physical functions of the bladder and bowels From careful consideration of the vast amount of human material available for study it becomes increasingly evident that alcohol in excessive amounts is the most commonly utilized technique employed to accomplish unconsciously an escape from mature responsibilities

Limitations of Chronic Alcoholism

The understanding of chronic alcoholism has been impeded much by the heterogenous collection of clinical material loosely designated alcoholic Not nearly every man who gets drunk occasionally is an alcoholic Furthermore in psychiatric territory there are many patients paretics in the early stages mildly depressed patients manics psychopathic inferiors morons and many others who may drink alcohol to excess and yet are not alcoholic Alcoholism bears about the same relation to the basic situation as does headache to brain tumor It is a symptom This brings up the important consideration as to the clinical evaluation of chronic alcoholism This will be discussed in the following pages under various headings

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Nature of Chronic Alcoholism

We do not believe that chronic alcoholism has a somatic pathology In spite of the wealth of organic morbidity in alcoholism its specificity is more in question today than ever before Liver cirrhosis one of the important supports of the pathology has not survived very well the inquiries of scientific research Researches into the chemistry of the vitamins has made further inroads into the postulated pathology of alcoholism Possibly in delirium tremens polyneuritis and other conditions the vitamin deprivation is a more essential condition than the alcohol

While there are a number of psychoses determined by alcohol yet in our opinion chronic alcoholism is not a psychosis The transitions into unreality are too abrupt and repeated too frequently For a long time the contact with reality is too tenuously held and is much more reminiscent of a psychoneurosis than a psychosis

In effect we believe that chronic alcoholism is a psychoneurosis Further it is the psychoneurosis of the introvert the shy reserved diffident individual who tends to be socially awkward and acquires social facility and graces only with the greatest difficulty At some time in his life he desires above all things social ease and popularity Soon he discovers that a few cocktails or other alcoholic beverages will melt away his reserves and not only will he feel more secure socially but he will even begin to enjoy the society of his fellow men

Thus the alcohol is used to escape reality just as psychoneurotic symptoms unconsciously are employed for the same purpose This becomes very evident in observing the large segment of unconscious rationalization in the psychoneuroses and in alcoholism alike

The psychoneurotic is sick and cannot meet the requirements of every day reality because of headache ear noises vertigo nausea vomiting tachycardia which are functional i e founded in emotional conflict and not in structural pathology When he gives his reasons for his excessive drinking the chronic alcoholic exhibits extreme rationalization He drinks because he has had financial losses because his health is poor because his wife nags him because his children disobey because the weather is cold and damp etc. These rationalizations like the symptoms of the psychoneuroses constitute screens unconsciously utilized to prevent an honest facing of real basic issues

Finally, fairly frequently we have observed the substitution of psychoneurotic symptoms for periods of alcoholic excess and vice versa This possibility needs to be kept in mind

Etiology of Chronic Alcoholism

Akin to the psychoneuroses the basis of alcoholism is emotional immaturity and again reminiscent of the psychoneuroses the roots of the immaturity are in childhood The careful study of our records show a common childhood situation in our alcoholic patients parental dominance usually loving dominance Deprived of the right and practice of learning to make decisions emotional growth lags and when adult years are attained the individual is illy equipped for the give and take of personal and social relationships He becomes nonplussed thwarted and frightened Soon he discovers temporary confidence and security in alcohol and then alcoholism is in the making

The psychoanalytical school believes that alcoholism is derived from latent homosexuality Unquestionably a certain segment of alcoholism has such an origin We think it is a limited segment We think much more usual is latent heterosexuality This is part and parcel of the emotional immaturity a casual flitting about sexually constituting an evasion of the mature responsibilities of home life in its various relations

Identification of the Alcoholic

Apparently because of the insult to his ego the acceptance of the fact often obvious to everyone else that he is a pathological drinker is exceedingly difficult Since pathological drinkers are recruited from the ranks of social drinkers it is important to note the signs of beginning addiction and to heed their significance The volume of alcohol consumption increases the hours of the day which formerly were non-drinking hours are progressively encroached upon by repeated libations of alcohol the individual begins to outdrink his companion and particularly just before the group leaves he imbibes a number of drinks in rapid succession the potential alcoholic begins to take morning drinks and to drink alone

When these departures from the social drinking pattern become frequent and serious the drinker is in a fair way of becoming a chronic alcoholic a man who cannot face reality without alcohol and whose adequate adjustment to reality as long as he uses alcohol is impossible

THERAPY OF CHRONIC ALCOHOLISM

While pharmacology has an important role in the treatment of the complications of alcoholism it is extremely doubtful whether drugs may ever be expected to cure the alcoholism itself

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his of alcoholic thoughts by attempting to repress them but by reviewing each time the entire sordid and distressing sequel in the past to taking one drink *negative* consisting of habituating the patient to thinking in terms of the many life satisfactions which are non alcoholic

4 *From his very first interview with the patient the therapist de clines to deal with him on anything but a mature basis* Therefore the patient must learn to make his own decisions If as often happens the patient asks for decisions as to whether he should remove all the alcohol from the house serve cocktails to guests keep away from the club or the taproom the answer is to do whatever he thinks best

5 *It is important psychologically that the patient comes to a true understanding of why he wishes to get well* *It is not as so often he believes* sincerely and erroneously believes because of the unhappiness and distress his habit has brought to his wife and family to his old mother and father and to his friends He wants to get well for himself These emotionalized rationalizations are genuine and the *remorse is very keen* but they do not lead to *recovery* Actually the *remorse is borne until* the suffering becomes *too severe and then it is drowned in the tidal wave* of a prolonged alcoholic debauch

6 As the history is worked out by the patient and therapist the patient comes to the appreciation and conviction that *his future must be non alcoholic* *In those patients who are destined for recovery* this conviction becomes very strong It has been said that should the in dividual be welcomed at the heavenly gates by St Peter proffering a cup of heavenly ambrosia he would reject it on the suspicion that it might contain alcohol

7 *Sometimes relaxation is used in order to minimize the effect of distracting alcoholic thoughts and the inhibitions they produce and to enhance the effect of direct suggestions* The patient is put into a state of abstraction He is asked to close his eyes breathe slowly and to think *of the prominent muscles when they are mentioned as becoming relaxed The cadence of the voice is made increasingly monotonous ending* with the suggestion that the patient is *drowsier and sleepier* This is con tinued for a few minutes and then an equal amount of time is spent *in* implanting simple constructive ideas

Re educational

1 *From the beginning and throughout the treatment the patient is* asked to read authoritative books and *notes on the psychopathology of* alcoholism and to make notes of his opinions in agreement or disagree

For convenience the treatment may be divided into four categories (1) the rules (2) psychological aspects (3) re educational (4) physical

Rules

Any plan of treatment which depends largely upon the cooperation of the patient must lay down a few conditions

I On the patient s part as a condition of treatment there must be at least understanding of the alcoholic situation some recognition of a need for help some desire to be helped Therefore any bullying over persuasion or tricking the patient into taking the treatment should be discouraged If the patient agrees to accept treatment perhaps because his wife has threatened him with divorce or his father with disinheritance unless he does so then the re educational plan is doomed to failure

II An honest willingness to try to remain abstinent from alcohol Of course there is no attempt to extract promises or to obtain pledges

III Frankness in all dealings with therapist

IV The patient must agree that if a relapse occurs he will notify the therapist or see that he is notified as soon as possible

The analysis of a relapse the conditions under which it occurred and the situations which seemed to precipitate it has much treatment value In a recovered group of patients irrespective of the duration of the alcoholism the number of relapses averaged less than three per patient

Psychological Aspects

1 It is psychologically important that the attitude of the therapist be unemotional impersonal and objective The patient has lived in a very different atmosphere He has been constantly watched praised and blamed rewarded and threatened At first he is nonplussed at the attitude of the therapist He expects and hopes to be treated as a child not as an adult Later he is appreciative of the new situation

2 While the alcoholism is the bull s eye of the psychological treatment target yet as the therapist retraces with the patient his life history many concentric psychopathological circles are hit Usually a pattern of *emotional immaturity* appears It has its sources in a parent childhood relationship in which the opportunities to develop emotional maturity security and decision were wanting The cure of the alcoholic is incidental to helping the patient attain a reasonable amount of emotional maturity

3 The production of conditioned thinking reflexes *Positive* which when it has been acquired leads the patient not to respond to the stimu

III While the patient should have a normal amount of exercise it is important to counsel him against serious overfatigue. Sometimes a patient unconsciously overtires himself in order to accomplish a rationalization for drinking.

IV The eating habits of the alcoholic are atrocious and his nutrition is bad. Encouragement to eat a well balanced diet at regular times is helpful.

V In a segment of alcoholic patients blood taken at certain periods during the day shows low blood sugar levels. These periods are more or less coincidental with the appearance of a great variety of subjective sensation. These sensations stimulate the patient to take large amounts of alcohol unconsciously meeting a carbohydrate need. This may be used advantageously in treatment by suggesting that late in the morning and afternoon the patient eat a bar of chocolate, a few cookies or pieces of candy.

VI It is important to be sure that the vitamin needs of the patient are supplied adequately.

Antabuse

There has been a great deal of interest in the new preparation known as antabuse, chemically tetraethylthiuramdisulfide. The drug is toxic but patients who take it regularly become sensitized to the ingestion of alcohol which, when taken, produces violent vasomotor reactions, palpitations and emesis.

Antabuse should be given only under carefully controlled clinical conditions. The usual dose is ½ a gram three times a day for two or three days and then ½ a gram daily. The average dose is ¼ to ¾ of a gram a day. Between the fifth and the eighth day a test is made with some alcoholic beverage, usually whiskey, in order to demonstrate the effect of the antabuse upon the patient. A syringe containing an intravenous preparation of vitamin C should be immediately available because a violent reaction may occur which can be controlled by a dose of vitamin C of 1 000 mgm.

The patient should continue the medication and complete cooperation, usually including the family, is necessary. The family also should be warned that patients may conceal the tablet under the tongue and expectorate it, or that they may deliberately produce vomiting in order to get rid of the medicine. In any instance psychotherapy should be used along with the antabuse and all in all antabuse has a limited area of

ment This procedure encourages a detached and independent viewpoint and the notes provide a helpful basis for discussion

2 Since the patient makes his own decisions he is not directed to do anything but among other things he is encouraged to make out each night a schedule of the following day s activities Cooperative patients arrange the schedule so that unoccupied time in which there is the likelihood of relapse is avoided Avoidable deviations from the schedule provide a useful therapeutic basis for discussion

3 It is fallacious to believe that a change of occupation can cure alcoholism There are no occupations which are free of opportunities for imbibing Furthermore no one ever solved a problem of addiction to alcohol by attempting to find an occupational alcohol dry dock However it may be that the occupation in which the patient is engaged is not a suitable one for him perhaps because it is beyond his limitations and capacities or because he dislikes it Avocations too are important and the patient is helped if he can develop an interest in hobbies particularly those which include manual craftsmanship

4 While again his course of conduct is not dictated it is encouraging if the patient decides to adopt a frank attitude toward his friends and tell them without evasion why he no longer is drinking In keeping with the mature level upon which the therapy is being conducted it is necessary to obtain the cooperation of the wife and family in order to persuade them to relinquish the childish attitudes and method of entreaty blame praise and constant watching

Physical

While it is true that the habit of alcoholism cannot be cured by pharmacological agents yet the physical aspects of therapy are extremely important adjuncts

I In every patient there must be a thorough physical examination and an effort to put the patient at his somatic and functional optimum

II The question of hospital or sanitarium care is important Perhaps one third of our patients are able to avoid a stay in hospital or sanitarium The remainder because of nervous depletion with markedly impaired resistance against taking alcohol require a period of hospital treatment Hospital residence should not be continued any longer than is absolutely necessary It is very easy for the hospital or sanitarium to become a surrogate for parental or wifely or family care and decision Because the desire for alcohol disappears the patient develops a false sense of security The main engagement against alcohol must be fought on the terrain of everyday life

III While the patient should have a normal amount of exercise it is important to counsel him against serious overfatigue Sometimes a patient unconsciously overtires himself in order to accomplish a rationalization for drinking

IV The eating habits of the alcoholic are atrocious and his nutrition is bad Encouragement to eat a well balanced diet at regular times is helpful

V In a segment of alcoholic patients blood taken at certain periods during the day shows low blood sugar levels These periods are more or less coincidental with the appearance of a great variety of subjective sensations These sensations stimulate the patient to take large amounts of alcohol unconsciously meeting a carbohydrate need This may be used advantageously in treatment by suggesting that late in the morning and afternoon the patient eat a bar of chocolate a few cookies or pieces of candy

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usefulness There have been fatalities reported from the use of antabuse Glud reports myocardial failure coronary disease, cirrhosis of the liver and other types of liver damage due to antabuse There should be a careful review of the somatic situation in regard to the liver, the presence of nephritis convulsive disorders thyroid disturbances or drug addiction before giving antabuse While the patient is taking antabuse paraldehyde is contraindicated as are the various elixirs and tinctures, in fact, any preparation containing alcohol During the period of treatment the patient should have frequent checks of the hematopoietic system in order to guard against complications in the blood forming organs It is the author's opinion that the drug has its usefulness in the total treatment of alcoholism but that the area of usefulness is limited, and the administration of antabuse must be surrounded with much precaution

Psychiatrists using antabuse in the treatment of alcoholics appear to be divisible into three groups a group which is quite honestly frank to them and except for definitely psychotic patients, tells them about antabuse how it acts and why they are giving it to them, a group that gives the drug without explanation, a group that lies in telling them that they are receiving a drug to help their general condition often saying they are giving them a vitamin pill daily To a non psychiatrist as is the editor this last practice seems indefensible one which will and should eventuate in the patient s losing confidence in his doctor To the editor the second practice seems undesirable" H A Christian

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CHAPTER XXXVII-B

DRUG ADDICTION

By HAROLD D PALMER

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difference between addiction to opium derivatives morphine heroin dilaudid codeine etc and addiction to other drugs is that it embraces three intimately related but quite distinct phenomena — namely tolerance habituation and dependence

Definitions — Himmelsbach defines these terms as follows

By *tolerance* is meant the gradual decrease in the effect produced by repeated administrations of a drug or conversely a gradual increase in the dose necessary to produce the same effect as did the initial dose It *is probably true that tolerance ultimately becomes of such magnitude* that the effect of the initial dose cannot be reproduced by excessive doses The mechanism of tolerance is not known

By *habituation* is meant the psychical phenomenon of adaptation to the repetition of an effect Habituation to the phenanthrene derivatives of opium probably is more intense than other forms of habituation In a sense habituation represents psychical dependence

Dependence is the term used to denote the distortion of normal physiological processes which results from prolonged abuse of morphine derivatives and which is manifested by the necessity for the presence of an adequate amount of one of these drugs in the body for the maintenance of physical normality The presence of dependence can be established only by the appearance of the characteristic syndrome of abstinence phenomena subsequent to withdrawal of drugs capable of maintaining dependence In a sense dependence represents physical habituation Since dependence to drugs other than the phenanthrene derivatives of opium has not been demonstrated satisfactorily probably it is safe to consider dependence as peculiar to this group of narcotics

The Magnitude of the Problem

The problem of drug addiction in the United States is one of considerable magnitude It has always been difficult to obtain accurate data on the number of drug addicts but the older estimates that there are upwards of one million drug addicts at large in the general population seem to have been gross exaggerations and have been pretty well disproved by more careful study According to the most accurate statistical accumulations in recent years it would appear that less than one tenth of one per cent of the general population is addicted to habit forming drugs This would mean that probably no more than 100 000 persons in the U S were addicts These statistics compare rather unfavorably with some of the other countries Great Britain for example has remarkably few chronic users of opium and other habit forming substances as have also

INTRODUCTION

The habitual self administration of drugs of any type whether they are taken for the relief of nervous tension insomnia mental depression pain or any other condition may constitute a true addiction For many the term drug addiction is applied only to persons addicted to the use of opium and its derivatives or to the users of cocaine while others include other habit forming drugs Now for many years the more careful restriction on the growing of the poppy plant and the manufacture of the derivatives of opium the more cautious and conscientious prescribing of habit forming drugs by the medical profession the stricter demands for the registration of all persons professionally handling habit forming drugs and the enforcement of the laws regulating the distribution of narcotics have combined to reduce the incidence of drug addiction in this country Medical groups and government agencies have cooperated splendidly in the establishment of treatment centers for problems of addiction In 1929 there was established two United States Public Health Service Hospitals one in Lexington Kentucky and the other in Fort Worth Texas for the treatment of addiction Until recently however few states have paid much attention to other sedative and analgesic drugs The use by the public of coal tar derivatives some of which when used by susceptible individuals undoubtedly are habit forming rapidly rose to alarming proportions With their appearance in increasing numbers in the courts jails and hospitals we finally became aware of the frequency with which persons become addicted to these substances and recognized the real danger of indiscriminate and unrestricted use of these drugs The degree of habituation to these substances rarely if ever reaches the intense proportion seen in morphine and cocaine addiction Yet the number of suicides accidental overdoses the increasing occurrence of chronic dependence on these drugs and the occasional appearance of true addiction to the coal tar derivatives has led to the creation of restrictions on their sale by many states

ADDICTION TO OPIUM AND ITS DERIVATIVES

Addiction to narcotic drugs differs rather distinctly from addiction to drugs of other types Himmelsbach has pointed out that true addiction is a condition developed through the effects of repeated actions of a drug so that its use becomes a necessity and cessation of its action causes mental or physical disturbances that is abstinence phenomena The

form of cigarettes or "reefers" which produce a combination of intensely unpleasant symptoms plus a bizarre delirium of transient nature

When the narcotic habit has fastened itself upon the victim it not only impoverishes him morally and physically but soon destroys his economic stability This comes about partly because of the destruction of working capacity but comes in no little measure also from the exorbitant cost charged by the purveyors It is known for example that the average price of the drug sold by the legitimate pharmaceutical dealer approximates $15 00 an ounce but the dope peddler not uncommonly gets $ 00 or more per ounce Even then the peddler gives a poor bargain because as the substance passes from one member of the ring to another it is adulterated sometimes to less than 10 per cent of its original strength

While it is true that the largest proportion of addicts occurs in the socially depraved individuals yet many drug addicts come from the professional fields Treadway observes that those individuals of higher standing both intellectually and professionally *tend to be the more or* less standardized addicts who are accustomed to small doses of the drug which are kept constant over a period of years Those tending to increase the dose are found more often among the irregularly employed *unstable the floating and racketeering population of the community* The migratory habits and unfixed residence of this class are proverbial

The large centers of the population are the chief contributors to the ranks of addicts There is possibly a higher percentage of negro addicts than whites Males predominate in a proportion of about 4 to 1 Social status is as might be expected extremely unstable Broken homes through divorce and separation are common About 57 per cent of addicts apprehended are under the age of 40 and there are relatively few after the age of 60 Drug addiction is found in each age group above 15 years with a greater concentration in the 25 to 45 year groups

Psychoses due to drug addiction are rare Hospital statistics in the United States show that about 0 15 per cent of all mental cases under treatment are due to or associated with drug addiction In Germany the estimate was put at 0 04 per cent Certainly drug addiction is less significant than alcohol in the production of mental disease The change produced in the mind of the narcotic addict is not so much a mental disease or insanity as it is a moral deterioration Added to this personality *change is a psychic factor which results from the attitude of abhorrence* with which society regards the addict and of which he is at least partially aware It is not unsound of course to postulate an organic deterioration as well due to the toxic effect of the drugs on the nerve cell Late in the course of an addiction there is undoubtedly some destruction of nerve

the Scandinavian countries In Germany before 1928 there were between 4 000 and 6 000 addicts in a population of 64 million but since that time there has been a rapid increase to a point where the number far exceeds that of any other European nation It is impossible of course to make any estimate as to the users of cannabis indica in Southwestern Asia and Africa or the prevalence of opium smoking in the oriental countries It has become known recently that in the modern refined technique of warfare the spreading of drug addiction among the enemy populace is a measure leading to gradual moral and physical disintegration preparing the way for more direct military conquest Accounts have appeared in the newspapers and elsewhere showing that the Japanese have encouraged openly the free use of opium and its derivatives among the Chinese and have produced limitless quantities for distribution in other countries The production and distribution of opium and its derivatives is a profitable illegitimate business all the way from the grower of the poppy plant to the vender in the street Huge narcotic rings protected by almost limitless money and connived at by bribed authorities have operated successfully in this and other countries

The Nature of Drug Addiction

The nature of drug addiction is difficult to define because constant and excessive use of coffee tea and tobacco is addiction of a sort Likewise the reliance on bromides aspirin and sedative drugs can be looked upon in some cases at least as a form of addiction In general one differential point seems to be that those drugs which produce euphoria or elation i e morphine opium cocaine etc are most likely to bring about a true addiction On the other hand those drugs which only allay feelings of depression or emotional tension or which alleviate chronic or recurrent discomfort and insomnia might not be called true addiction The trap into which the user of the opium products falls is one of temporary elation due to the drug Its first euphoria is followed by depression and unpleasant physical sensations in the digestive system and extremities and these in turn lead again to renewed use of the drug in larger doses in order to capture the original elated state Finally the drug is taken only to relieve the intense depression and the physical pain due to abstinence since the euphoric effect long since has failed to appear There are certain drugs which seem to lie mid way between the depressant substances such as bromides barbituric acid derivatives etc and the opium products The chief one is cannabis indica which is known also under the name of mariahuana Mariahuana usually is smoked in the

of inadequacy since only under the narcotic can they have the subjective feeling of well being and superiority The psychopath who is morally weak and possesses no inhibitions upon his acts has only the criteria of pain or pleasure upon which to base his conduct He desires pleasure and derives it from the drug and feels no restraint in taking it

Kolb distinguishes between two types of pleasure sought by the addict one which he calls positive pleasure or that which results from rising above the usual emotional plane and the other which he calls negative pleasure or that which follows relief from pain and anxiety He feels that after the first stage of addiction during which tolerance and dependence are established the positive pleasure disappears and the motive for continued use of drugs becomes purely the avoidance of discomfort and pain Kolb also believes that relapses are due usually to an attempt to regain the sense of pleasure originally experienced

As the use of the drug progresses a fatalistic or resigned attitude usually is developed by the addict since he feels that conflict and suffering must be avoided at all costs Some rationalization of his addiction is necessary to provide sufficient mental comfort to make his life bearable The addict then either can increase the dose over and above physical requirements in an attempt to recapture the original sensation of pleasure or he may adjust at a level of moderate use and continue it for years only as it is needed to relieve the physical and mental discomforts of abstinence or withdrawal The treatment problem therefore involves not only enforced withdrawal but psychological reeducation aimed at the achievement of emotional maturity self sufficiency and freedom from neurotic tensions and strains Treatment is therefore directed at the fundamentally causative personality defects

Kolb s Etiological Classification

Lawrence Kolb Asst Surgeon General of the U S Public Health Service has drawn up a valuable etiological classification of drug addiction Pescor has made a study of the value of the Kolb classification of drug addicts as applied to patients undergoing treatment for drug addiction at the United States Public Health Service Hospital in Lexington Kentucky The data for this investigation were secured from the clinical records of 1 036 patients admitted to the Lexington Hospital during the year July 1 1936 to June 30 1937 Percentage frequencies for the various factors were computed according to their occurrence in the whole group of 1 036 patients and in the subgroups corresponding to the Kolb classification which consists of the following major categories

tissue and this may lead to interference with intellectual functions and perhaps ultimately to a form of dementia

The Causes of Addiction

Drug addiction like alcoholism is the result of a defect in the personality of the individual It can be looked upon as a symptom of inadequacy and instability rather than as a cause The user of narcotics is a chronically maladjusted emotionally immature person who has sought the effect of narcotics to deaden the impact of reality A survey recently made by Treadway indicates that among the relatively small numbers of addicts coming from the group of persons licensed to deal in narcotic drugs for professional or business reasons more than three fourths attribute their addiction to previous use of narcotics in prescribed medical treatment or in self treatment for the relief of pain Among the illegitimate handlers the majority attribute their addiction to association with other addicts or to a desire for an experience to satisfy curiosity to obtain a thrill or allay emotional distress A few of this class attribute the habit to previous use of drugs in prescribed medical treatment or to self treatment for the relief of pain insomnia emotional distress etc

It is best not to consider drug addiction as a disease but rather as a symptom of underlying personality defect on the basis of intellectual insufficiency lack of adequate emotional control faulty habit training or maladjustment of the instinctive life In many instances morphine and opium are resorted to by the psychopath who is not adequate to the demands of life Drug addiction may develop on the basis of personality defects of any type however and we have seen cases in which addiction is dependent upon a depressive state melancholia psychopathic inferiority mental deficiency and occasionally as a means of facilitating the separation from reality in the schizophrenic Careful examination of the life history of the addict indicates emotional instability immaturity and spoiling inadequate discipline etc There can be no doubt but that the addict is dissatisfied with himself as he is has made a painfully unsatisfactory adjustment to life and seeks the artificial aid of drugs to achieve even momentary freedom from his inadequacy

With the exception of the normal individuals accidentally addicted to drugs the whole group represent types who were adjusting to life with great difficulty before they became acquainted with the narcotic The psychoneurotic may take the drug to relieve himself of his inner tensions of his somatic complaints The psychopath and those of borderline intelligence utilize the drug as a stimulant to rise above their usual level

and would have two or more children His social adjustment would be acceptable despite his addiction He would have no history of military service His family history would be negative for psychopathic determinants His parents would have been in comfortable economic circumstances They would have maintained average discipline in the home during the patient's developmental period

His past medical history would be positive for some chronic disease during adult life but would be negative for venereal disease Physical examination would reveal the presence of diseases of the circulatory system genito-urinary system or joints singly or in combination His physical ailments either would cause his death or would be of such severity as to require more or less permanent infirmary care If he lived he would be a very cooperative patient a willing worker but unable to do much work because of his physical handicap His insight would be excellent He would maintain that drugs were harmful from every standpoint The prognosis would therefore be above average Upon release from the hospital he would plan to return to his family and would have some sort of employment commensurate with his physical ability

Psychopathic Diathesis — Patients identified as showing psychopathic diathesis might very well be termed average addicts since they constitute 54 5 per cent of the group studied The only criterion which tends to distinguish such patients from average addicts is the rationalization for addiction namely curiosity and association with addicts. Pescor would change the term psychopathic diathesis to *hedonistic personality* since addicts in this category are primarily pleasure seeking in type Their fundamental defect is an ill-defined emotional instability which finds expression in a search for new thrills excitement and pleasure

The statistical representative of the whole group of patients as well as those with psychopathic diathesis may be described as a white male prisoner 38 years of age given a 2 year sentence for the illegal sale of narcotics His family history would be positive for such familial conditions as cardiac diseases tuberculosis or cancer and if any psychopathic determinants existed most likely they would be alcoholism or drug addiction His parents would be in marginal economic circumstances average disciplinarians and the family relationships would be congenial *The patient would be one of several children a native of native parentage* the parental home would be intact until he was 18 years of age and the childhood adjustment apparently would be normal He would be brought up in a religious faith but would discontinue church affiliations as an adult He would graduate from the eighth grade taking up an occupation

(1) *Normal individuals accidentally addicted* This group includes persons of normal nervous constitution accidentally or necessarily addicted through medication in the course of illness

(2) *Psychopathic diathesis* This group includes individuals who show psychopathic dispositions or tendencies characterized by behavior resulting from misinterpretations of environmental settings or situations but not a well crystallized personality defect

(3) *Psychoneurosis* This group includes individuals suffering with the ordinary types of psychoneurosis

(4) *Psychopathic personality without psychosis* This group is composed of persons who show deviation of personality usually expressed as constitutional psychopathic inferiority psychopathic personality or constitutional psychopathic states where volitional and emotional control are distorted gravely from the normal

(5) *Inebriate* This group includes individuals in whom alcoholic indulgence either periodic or more or less continuous played an important rôle as a precipitating factor in the addiction They apparently have a so called inebriate impulse

(6) *Drug addiction associated with psychosis* This group includes addicts suffering with frank psychosis organic toxic or functional

Pescor s evaluation of the classification is of such usefulness that it deserves complete publication here

Normal Individuals Accidentally Addicted — Normal individuals accidentally addicted are a distinct minority as far as this study is concerned Only 3 8 per cent of the total number of patients studied were thus classified As a matter of fact even this low figure probably is too high

From a statistical standpoint the most typical representative of the normal group would not become an addict until after the age of 40 He would be given morphine legitimately for the alleviation of a painful or distressing physical condition and would confine himself to the use of that drug The period of addiction would be less than 2 years but it would be continuous unbroken by any attempts at cure of either a voluntary or compulsory nature Currently this statistically typical representative would be either a voluntary patient with no antisocial record or a first offender sentenced for violation of the Harrison Narcotic Act He would be a native American of native born parentage 60 years of age or older His childhood adjustment would be normal He would have a primary grade school education He would come from a rural community and his occupation would be farming He would be a steady worker in marginal or comfortable economic circumstances He would be happily married

and agreeable As the time for his release approached he would maintain that he was through with drugs forever because he did not want to spend the rest of his life in jail indicating that he still thought drugs were beneficial but that the penalty outweighed the benefit He would plan *to live with responsible relatives largely at the insistence of the hospital* officials However he would have no offer of employment to look forward to He would be given an average prognosis for permanent cure which is a vague way of stating that probably he would relapse

Psychoneurosis - Psychoneurotic patients account for 6 3 per cent of the total number of patients studied From a statistical standpoint a typical psychoneurotic would give therapeutic necessity as an excuse for his addiction Morphine would be the first drug used the drug of choice the only drug used and of course the last drug used He would make two or more voluntary attempts to break his habit but would give no history of compulsory treatment He would relapse to the use of drugs after each voluntary treatment because of therapeutic necessity or because of environmental stress and worry He would have no antisocial record He would come to the hospital as a voluntary patient

As a child he would be considered a studious shut in good boy type He would have a college education and would be engaged in a professional or semiprofessional type of occupation from which he would derive a *modest income He would live in a rural or semirural neighborhood* He would be congenially married His social adjustment on the whole would be considered acceptable despite addiction He would be a World War veteran

The parental home would have been intact during the patient s developmental years The parents would have been in moderate economic circumstances His past medical history would reveal chronic diseases during childhood and either neurotic tendencies frank neuroses or unspecified nervous breakdowns during adult years Physical findings would include disease of the digestive tract defective vision and diseases of the respiratory tract alone or in combination In other words he would have some chronic condition which would not be serious enough to require infirmary care He would have a mental age of 15 years or over He would be uncooperative demanding his release and eventually would be discharged against medical advice He would be unpopular both with his fellow patients and custodial officers because of constant complaining about his physical ailments and of his tendency to shirk work He would still believe that drugs were beneficial but that the loss of social esteem and the danger of legal entanglements outweighed the benefit He would receive intensive psychiatric treatment during his period of hospitalization

classified in the domestic and personal service As an adult he would live in a deteriorated metropolitan section More than likely he would have to resort to illegal means of earning the additional income required to support his drug habit He would marry but this marriage probably would terminate in separation or divorce He would have no children possibly because drugs deprived him of a normal sexual urge He would probably make a satisfactory social adjustment prior to addiction but not after addiction He would be tolerant towards all forms of vice occasionally indulging in all forms He would not give a history of military service

He would become addicted to morphine at the age of 27 through the influence of associates and curiosity He would use more than one narcotic drug but would prefer morphine when it was obtainable The last drug used therefore most likely would be morphine He would have been addicted about 10 years Probably he would give no history of voluntary attempts at cure would admit at least one enforced treatment in a jail or penitentiary but would not remain abstinent any longer than 2 years at the most relapsing because of association and desire to recapture the pleasant sensations produced by the drugs

His first arrest would occur at the age of 28 for violation of drug laws for which he would have an equal chance of being acquitted or sent to the penitentiary He would not have a delinquency record prior to addiction After addiction his offenses more than likely would be confined to violation of drug laws for which he would be given at least one penitentiary sentence and at least one jail sentence Probably he would have spent a total of 3 years behind bars on previous sentences

He would give a history of the usual childhood diseases without complications but as an adult he would be subject to some chronic disease such as heart trouble arthritis tuberculosis or asthma He would deny any mental disorders but if he did admit any it would be a tendency toward neurosis However he would admit readily a history of gonorrhea Ninety nine chances to one he would have poor dentition either caries or pyorrhea alveolaris there would be also a strong possibility of defective vision However his physical defects would not prevent him from doing manual labor The psychologist would probably give him the Army alpha test which would disclose that the hypothetical patient had a mental age of 13 years 8 months

During his stay in the institution he would abide by the regulations show a good knowledge of his occupational assignment and would be a willing worker He would be accepted by his fellow patients and would like to work with them The custodial officers would find him pleasant

through the alcoholic route in less than a year after each treatment He would have no history of previous misdemeanors and would be a voluntary patient at the hospital He would come from a rural or semirural neighborhood His family history would be positive for alcoholism and of course he himself would be strongly addicted to alcohol He would have minor physical ailments but would be able to do manual labor In all other respects he would not differ from the average addict described under psychopathic diathesis

Drug Addiction Associated with Psychosis — Only one patient in the *entire series was classified in the category of drug addiction associated* with psychosis A number of individuals developed psychoses while hospitalized but since they did not become addicted as a result of their psychoses they could not be included in the present category Needless to say no comparative data can be presented for one case The patient in this case was an elderly individual who became addicted to morphine after the age of 60 while suffering from a psychosis diagnosed as simple senile deterioration He took the drug of his own accord to set his mind at rest

It is quite obvious from this thorough going study made by Pescor of more than 1 000 cases of drug addiction that the Kolb etiological classification is of great value It emphasizes the importance of a thorough history personality study and total evaluation of physical and psychological factors in the study of drug addiction Statistical records have been very unsatisfactory in the past since most treatment methods had little time to devote to actual study of the patient before the treatment was undertaken

Opium Addiction

Addiction to opium smoking is thought to be rare except in the oriental colonies of large American cities In such colonies opium smoking dens are available to Oriental and Occidental alike The vivid pictures of the Chinese opium den of fiction perhaps are overdrawn but in the main the essential facts are borne out by addicts A pipeful and a few hours of isolation and pleasure can be bought for a dollar or two The first reaction to opium smoking is one of violent nausea splitting headache and profound depression with occasional physical collapse After the initiation of a dozen pipesful the smoker experiences great happiness and pleasure and the forgetting of unpleasant experiences with a loss of all disturbing sensations This state lasts for several hours and usually is followed by a few hours of sleep Waking from the sleep is not pleasant

Psychopathic Personality without Psychosis — Individuals given a diagnosis of psychopathic personality comprised 11 7 per cent of the whole group of patients To this were added several patients who were basically psychopathic but who developed frank psychoses during hospitalization and also three criminal psychopaths who claimed that they were not addicts The total representation of the psychopathic group in the present study is therefore 13 4 per cent instead of 11 7 per cent

The statistically typical psychopathic drug addict would rationalize his addiction on the basis of curiosity and association He would make no voluntary attempts to rid himself of his habit but would give a history of three or more compulsory cures However he would relapse after each cure through association with addicts and the effort to recapture the original thrill

His first arrest would occur before the age of 20 for grand larceny His antisocial record prior to addiction would include juvenile delinquency misdemeanors and convictions His antisocial record after addiction would include misdemeanors and convictions not only for violation of drug laws but for violation of other laws as well He would have a record of two or more previous convictions and three or more misdemeanors for which he had spent 2 or more years in jails or penitentiaries

He would be a prisoner patient single either of foreign born parentage or else foreign born himself His parents would be in marginal economic circumstances The parental home would be uncongenial and characterized by rather loose family ties He would live in a deteriorated city environment As a child he would have shown definite antisocial tendencies As an adult he would make a living by gambling and by extralegal pursuits His social adjustment would therefore be poor both before and after addiction

His institutional adjustment would be so unsatisfactory that sooner or later he would be recommended for transfer as a detriment to the station He would be reported for violation of institutional rules custodial officers would consider him as queer or paranoid and he would be unpopular with his fellow patients Psychiatric treatment would be emphasized *The prognosis for rehabilitation would be considered poor*

Inebriate Personality — The inebriate personalities comprise the second largest group of addicts accounting for 21 9 per cent of the total number of patients studied The statistically typical inebriate individual takes to the use of drugs as a means of sobering up after alcoholic sprees Morphine would be his drug of choice as well as the first drug used He would have a history of two or more voluntary cures but would relapse

10 per cent carbon dioxide inhalations should be used In severe collapse the respirator may be indicated After a few hours a strong saline purge should be given

Morphine Addiction

Morphine sulfate is the drug used most commonly and consistently by addicts It is taken by the hypodermic method although some addicts who have built up enormous tolerance take the drug intravenously The daily consumption may vary between 30 mgm and 4 gm (gr ½ and 60) but the economic factor tends to keep the consumption well below 0 6 gm (gr 10) a day Addiction develops in a remarkably short period of time perhaps in some cases after not more than a dozen injections scattered over a period of a week or two

The drug at first produces a remarkable euphoria freedom from care and worry and mental ease which is most welcome to the victim Long standing feelings of personal inadequacy and loss of self esteem are replaced by feelings of power and limitless strength and courage This state is unquestionably the one which influences the individual to pursue the use of the drug in an attempt to keep such a pleasurable sensation intact as long as possible Soon however the euphoria fails to appear and there is set up an unhappy situation in which the drug must be taken for the relief of the abstinence symptoms As the use of the drug continues there is definite deterioration of the personality Character change becomes evident in a period of weeks after the beginning of morphine use Whether the drug is taken because of a psychopathic inadequacy or whether it is taken for the relief of unbearable pain due to cancer or one of the other agonizing physical conditions the alternation of personality becomes evident in a phenomenally short time Efficiency declines because of the deadening of higher intellectual functions because of the loss of physical energy and because of the disappearance of ambition and purpose The individual s entire thought and conduct revolve about the problem of securing the drug His self esteem suffers because of the realization that the habit has become fastened upon him and ethical and moral degeneration are evident in his dishonest attempts to deceive others and to obtain the drug through theft or criminal act The individual is untrustworthy in all categories is untruthful lacks all sense of responsibility Even those addicts voluntarily seeking help will deceive the admitting physician and nurse about the amount of drug he has taken often exaggerating as to the dose he has become accustomed to in order that his withdrawal will be begun at a much higher level In

being characterized by great malaise which more or less naturally leads the addict to seek further escape by means of the opiate The physical dilapidation of the opium addict is perhaps more marked than in other forms of addiction There is a yellow sallow parchment like skin chronic constipation mental apathy and depression, weakness emaciation and general muscular wasting The addiction to opium smoking usually terminates in the development of deficiency diseases pulmonary tuberculosis or degenerative processes The moral depravity is said to reach profound depths

Paregoric Addiction

Addiction to paregoric tinctura opii camphorata is far from rare Paregoric is drunk as a draft or mixed with some beverage The quantity of anhydrous morphine contained in paregoric is small 0 035 per cent and its sale without prescription is limited in most states to one ounce It may be resorted to by chronic alcoholics when alcohol is not available Druggists report that on Sundays when the bars and liquor stores are closed there may be a veritable run on the store by disreputable individuals seeking to buy illegal quantities of paregoric The class of persons resorting to this intoxicant are of the same level with in fact often the same individuals who buy rubbing alcohol for consumption They may go from drug store to drug store accumulating an ounce of paregoric in each until they have a sufficient supply to produce a stuporous intoxication to tide them over until the saloons are opened on Monday morning Paregoric is not a convenient nor profitable product for the regular narcotic venders to handle and rarely do true drug addicts resort to its use

Laudanum Addiction

Laudanum tintura opii is almost impossible for the addict to obtain through legitimate channels without a physician s prescription It contains a somewhat larger quantity of the active alkaloid 0 1 per cent of anhydrous morphine than paregoric The action sought by the addict is the relief of abstinence symptoms or the production of a semi stuporous confused hallucinatory state If paregoric or laudanum are taken by mouth with suicidal intent or by accidental overdose the stomach should be evacuated and lavage with potassium permanganate 1 to 1000 solution should be given Stimulation by caffeine in the form of caffeine sodium benzoate intravenously in 0 5 gm (gr 7½) doses may be required If medullary depression is severe artificial respiration and oxygen or 5 to

lary depression is severe enough to produce respiratory failure the patient should be placed in a respirator Oxygen or carbon dioxide inhalations can be used with good effect also The general management of morphine addiction is given later on under the heading Treatment of Narcotic Addiction

Heroin Addiction

Heroin is diacetylmorphine and usually is taken by hypodermic injection The psychic action of the drug is more marked than morphine especially the exhilaration and elation Likewise however the degree of depression following its initial effects is greater One addict differentiated between morphine and heroin stating that morphine is better for the long pull but heroin gives me a better ride Heroin is thought erroneously to have primarily an aphrodisiac action and it may be taken repeatedly in order to achieve a pathological degree of sexual excitation The habit leads to a rapid loss of sexual potency Heroin affects the higher psychic functions more quickly than morphine or opium and moral deterioration appears to be more rapid It has been chiefly among heroin addicts that we have noted the scars as the result of hastily injected hot solutions and it is also among heroin addicts that we have observed the greatest degree of deterioration In cases of accidental or purposeful overdose the emergency management is the same as for morphine overdose The general management of heroin addiction is given in detail in the section Treatment of Narcotic Addiction The withdrawal symptoms are likely to be more stormy and troublesome than in other forms of addiction

Codeine Addiction

Addiction to codeine occurs much more frequently than has been reported to date In Canada where until recently no restrictions were placed on the sale of codeine addiction to the drug is said to have become a grave problem Codeine occurs in natural opium and is manufactured by methylation of morphine and its chemical name is methylmorphine The borderline addicts are those tending to rely too much on the drug and constitute a great problem since it is felt that those individuals will change to the more potent morphine or heroin as soon as the narcotic craving set off by the codeine becomes intense enough

Shortly after the introduction of codeine into general medical use it was thought that its addiction properties were so low that the drug could

examining addicts applying voluntarily for admission to a large general hospital we have found supplies of morphine secreted in the body cavities blotters handkerchiefs shirts and other articles of clothing which have been saturated with morphine in solution and carefully dried

The addict is the victim of psychological conflicts and fears is weighed down by the social disapproval of his addiction and becomes furtive and suspicious irritable and difficult The attentiveness and powers of con centration of the addict deteriorate partly as a result of progressive restriction of interest to the sole problem in life that of obtaining the drug and partly due to the cellular injury brought about by the drug itself As stated previously mental symptoms or frank psychotic break downs rarely are associated with addiction If in the course of treatment or in short periods of abstinence hallucinatory episodes delirium or spells of excitement occur it is likely that the case is complicated by the use of some other toxic substance such as cocaine or alcohol A sudden and drastic withdrawal of the drug may lead rarely to hallucinosis but more commonly is accompanied only by extreme restlessness agitation and apprehension

Physical Symptoms — The color of the skin usually is sallow with an ashy gray appearance and the skin surfaces of the arms and thighs show the numerous scars of hypodermic injections Occasionally there are large areas of scar formation on the thighs or arms at the site of hastily given hypodermics where asepsis has not been followed or where hot solutions of morphine have been injected subcutaneously The addict in the acute stages of deprivation often cannot wait until the hot solution cools sufficiently and recklessly injects the liquid into the tissue Physical debilitation is obvious with loss of weight marked muscular hypotonia tremors disturbances of muscular coordination evident especially in speech or in disturbed functions of the eye muscles There may be general sensory impairment and parasthesias are not uncommon Sexual im potence is the rule Chronic constipation is present and there is complete anorexia The skin is dry the hair sparse and dry and usually there is *a rather marked degree of anemia Especially in periods of deprivation* there are joint and muscle pains neuritis and abdominal cramps

Deliberate overdose may be taken with suicidal intent and occasion ally accidentally overdose may be given in a desperate effort to recapture the thrill and the lift which the first few small doses produced The acute state of overdose calls for prompt use of stimulative and supportive measures as follows Caffeine in combination with sodium benzoate by hypodermic or intravenous injection should be given in 0 5 gm (gr $7\frac{1}{2}$) doses or strychnine sulfate 2 2 mgm (gr $\frac{1}{30}$) by hypodermic If medul

times described are bizarre distorted hallucinations often of diminutive character The Lilliputian hallucinations occur most commonly in this condition The cocaine addict becomes rapidly deteriorated both morally and intellectually begins to associate with persons of low character prostitutes petty criminals etc and may be led into or may initiate sexual crimes and acts of violence The habitual criminal not infrequently takes cocaine in order to stimulate his courage to commit homicide or some other criminal act In the vernacular many criminals have to get hopped up with a dose of cocaine before committing the crime As a result of habitual use of cocaine there is apt to be a marked and persistent sensory disturbance in the form of parasthesias Cardiac action is impaired there is marked loss of resistance to infection and the addict is particularly susceptible to tuberculosis and other low grade chronic infections If abstinence is forced the parasthesias become acute and there is a sensation of movement and creeping in or under the skin the so called cocaine bug Gastric disturbances depression and hallucinations may appear during the withdrawal phase Chronic paranoid and hallucinatory states occur in cases of longstanding habituation Bleuler has reported longstanding cases resembling Korsakoff s psychosis and others have reported chronic paranoid and depressive reactions In a recent survey of the problem of cocaine addiction it was found that very few persons took cocaine alone but usually used it in combination with heroin or morphine

The relation of cocaine addiction to sexual aberrations and criminal types is notorious It is often taken for the purpose of sexual stimulation and may be given surreptitiously to another person for the purpose of fostering sexual conquest The drug however defeats its alleged sexual purpose because its use soon produces impotence Compensatory pornographic interest may replace the lost sex power and it is stated by Diethelm that cocaine addicts usually prefer to take the drug in the company of other psychopaths and in such a company the conversation is composed of highly erotic and fantastic stories embellished by running accounts of hallucinatory experiences These snow parties often terminate in homosexual orgies Actors form the largest part of such cocaine rings The addiction occurs most frequently in younger persons from 16 to 22 and is spread by contagion the addict wanting to induce the neophyte to join in the thrill of the cocaine intoxication Deterioration is said to be less rapid than in morphine and heroin addiction but yet the direct effects of the drug are more destructive Particularly characteristic of cocaine addiction are the unstable temper the outbursts of violent anger the defective memory and the morbid sex and criminal tendencies

safely be administered for the relief of chronic intractable pain and it was thought especially valuable as a substitute for heroin in cases of chronic *cough from tuberculosis asthma or other chronic disorders* *The accumulation* of experience however has shown that the drug has definite addiction liabilities and that it must be prescribed with caution In an article on the subject of codeine addiction Davenport lists 32 cases of proven addiction while Terry *reported 83 addicts regularly using codeine and* 420 borderline codeine addicts Withdrawal of codeine in the treatment of addicts is characterized by diarrhea restlessness and insomnia

Dilaudid Addiction

Dilaudid is the trade name applied to dihydromorphinone hydrochloride a drug originally thought to be a non habit forming opium derivative which could be substituted for morphine It was suggested as an *anal*gesic in mitigating the withdrawal symptoms in morphine addicts but was found to possess addictive properties though it has somewhat less addiction liability than morphine or heroin The drug is approximately four times as effective in the relief of pain but its action is somewhat *shorter* than morphine Addiction to dilaudid has been reported though in general the addict switches to morphine or heroin to obtain the greater euphoric effect of the latter drugs The drug should be prescribed with the same caution as other habit producing narcotics

Addiction to Cocaine

Cocaine addiction is relatively rare but is encountered *occasionally* in combination with alcoholism or morphinism Addicts to cocaine are characterized by a very fixed and total dependence upon the drug and by the most pernicious and complete deterioration The drug is taken by *mouth in tablet or capsule form or may be put into solution* and taken by hypodermic injection The most common method, however is the sniffing of the powdered drug which is known among addicts as snow The literature contains an occasional report of perforation of the nasal *septum in cocaine sniffers or snow birds The first effect* of the drug is euphoria and excitement Pleasant states of fantasy may occur and the person feels mentally keen and intellectually alert This state is transient but during this time the individual is witty garrulous talkative full of all sorts of schemes and ambitions writes copiously and is oblivious to fatigue or hunger The condition is not unlike a hypomanic state but is followed quickly by profound depression and malaise Some-

for the treatment of drug addiction located at Fort Worth Texas and Lexington Kentucky

In the past the method of treatment required commitment to one of the federal penitentiaries Treadway states that repeated prison sentences have been imposed more often upon drug addicts than upon any other type of federal prisoner He found that approximately half of the narcotic addicts sentenced to the federal prison for the first time had been addicted to the drug for 11 years or longer and that 25 per cent had been addicted for 20 years or longer Only 25 per cent had been addicts for 6 years or less

The so called drug cures have been much abused and exploited Until the establishment of the Federal Narcotic Farm now the U S Public Health Service Hospital about the only public hospitals where addicts could obtain treatment were those with especially established drug wards for the study of the problem of addiction In general these were not particularly satisfactory because of inability to provide adequate supervision and because of the persistence of the underworld agents in keeping up contact with the victim It was not uncommon for the vendor to meet the addict on his way out of the institution in order that he could provide the cured addict with a small supply just in case Even the bona fide cured addicts were pursued and blackmailed With the establishment of the two Public Health Service hospitals for the treatment of drug addicts medical science accepted the task of study and treatment and the progress in the scientific management of therapy and rehabilitation has been most encouraging

There is undoubtedly some danger in the abrupt withdrawal of the drug in cases of long standing addiction who have become more or less firmly conditioned and in those who suffer impairment of cardiac function or severe debilitation Kolb believes that a fair number of unreported deaths must occur since he has definite knowledge of 11 fatalities Six of these occurred in 1 year in a hospital where 130 patients were given the hyoscine treatment Two received a modified Towns-Lambert treatment in which the specific and purgation were given without any morphine it being considered in the hospital where they were treated to be more or less sinful and criminal to give morphine to an addict One was a woman about 60 years old with a strong habit who was given abrupt withdrawal because it was thought somehow to be morally wrong to give morphine to an addict even in treatment One a man 62 years of age died under abrupt withdrawal (Information was not definite as to whether this man collapsed in a heat cabinet) One a man 42 years old with a possible but unproved heart lesion suddenly

In the acute stage of cocaine intoxication where the drug has been given to a non addict or where the addict has taken an overdose there may be a grave threat to life The immediate effects of such overdose are intense stimulation, marked vasoconstriction giving rise to icy coldness in the extremities anginoid pains or true coronary spasm a rapid small hard pulse dilated pupils and convulsive seizures If the drug has been taken by mouth the immediate treatment should consist of gastric lavage with tannic acid solution to precipitate the alkaloid Phenobarbital sodium or sodium amytal may be given by hypodermic or by rectum or if convulsions occur the barbiturate should be given intravenously amyl nitrite inhalations and oxygen may be resorted to in order to combat cardiac or respiratory failure The general management of the addiction is the same as that for morphine addiction The prognosis is poor not only because of the degree of deterioration but also because of the psycho pathic character originally leading to the addiction

Treatment of Narcotic Addiction

Abrupt withdrawal is greatly feared by the drug addict and this prevents many addicts from seeking medical help early enough in the course of their addiction to render the results of treatment hopeful Addicts speak with horror of the rigours of cold turkey the vernacular of addicts for abrupt withdrawal Most addicts ask voluntarily for help only after the drug has failed to provide them with the accustomed mental and physical relief they hope for Often the addict comes wishing merely to accomplish a reduction in the required dose so as to relieve the economic strain Obviously such patients present a poor prognostic risk Fortunately such insincerity is not the rule and the majority come with genuine intentions Thomas Parran surgeon general of the U S Public Health Service believes that most addicts want to be relieved of the habit but that only a few can afford adequate sanitarium treatment Punish ment by jail sentence or other punitive methods alone are never effective The urge for cure has been so great in some that they have pleaded guilty to crimes which they did not commit in order to secure treatment in the penitentiaries Parran believes that the addict is a sick person who has no place to go

Rehabilitation of an addict is a lengthy and expensive procedure in volving special treatment methods extensive occupational therapy help and psychological reeducation Addicts to opium cocaine cannabis indica peyote and to any preparations or derivatives of these four drugs are eligible for treatment in the U S Public Health Service Hospitals

distressing symptoms of withdrawal and was dangerous to life Rossium which appeared to have behind it an anaphylactic theory of drug addiction was studied extensively by Kolb and Himmelsbach They report that it has no specific helpful effect in bringing about the relief or the successful cure of the withdrawal stages The substance rossium was analyzed and thought by Himmelsbach to be a compound somewhat related to pyramidon

The general management of the addict is admirably summarized as follows by Kolb

Withdrawal — The abrupt withdrawal treatment has been used most commonly in the prison treatment of addicts One advantage of the treatment is that the discomforts and suffering are quickly over and the patient more rapidly returns to normal Undoubtedly there are present some dangers as previously stated Some of the specific treatments use abrupt withdrawal or withdrawal in from 4 to 36 hours Some addicts coming voluntarily for treatment have weak addiction habits and may be already partially cured Kolb observes that this condition has prevailed for a number of years and is growing more evident as time goes on partly because of the increasing difficulty in securing undiluted drugs and partly because physicians are becoming more and more reluctant to furnish narcotics to addicts even when they might consider the case to be worthy As a result of this situation only about 20 per cent of addicts have sufficiently strongly established habits when they come for treatment to warrant more gradual and cautious withdrawal Those with the weakly established habits do well under the abrupt withdrawal method combined with certain supportive measures such as sedatives in moderation hydrotherapy management of gastrointestinal symptoms and an occasional dose of codeine to relieve the abstinence symptoms during the first two or three days Providing the circulatory system is adequate this abrupt withdrawal method is most satisfactory in such types On the other hand in individuals with strongly established habits abrupt withdrawal may be dangerous and is unnecessarily cruel Such treatment often is given in prisons and sometimes in hospitals because of a feeling that the addict does not deserve any better treatment This attitude of course goes along with the general hostility toward addicts which is psychologically unfortunate and paves the way for relapse

In the gradual withdrawal method or the 7 day treatment after the patient has been stabilized on morphine the dose is reduced by one seventh each day for seven consecutive days In the even more cautious withdrawal such as the 14 day method after stabilization one fourteenth of the amount is withdrawn each day In the method of

collapsed under abrupt withdrawal Hyoscine belladonna and purgatives undoubtedly increased the distress of 8 of these patients and contributed to their deaths

Numerous 'special methods have been advanced over a period of years and they have been the subject of meticulous investigation by Kolb Himmelsbach Treadway Lambert Vogel and others Of these special methods the lecithin treatment of Ma and the insulin technique of Sakel seem to have some possible value The lecithin treatment advanced by Ma has as its basis the belief that the lipoid material in the body cells of opium addicts is reduced almost to nil and when lecithin is administered orally the lipoid material is increased gradually while the craving for opium correspondingly subsides Animal experiments have demonstrated however that there is no significant variation from the normal in the lipoid material in morphinized animals In a study in 1935 reported by Ma opium smokers were given 20 to 30 grams of soy bean lecithin by mouth three times a day after meals During this treatment they were allowed to continue their opium smoking in their customary way It is reported that the patients receiving this treatment showed a less and less desire for opium and eventually quit it The time for effecting a cure varied from 4 to 22 days The treatment has not been adequately tested yet although there are occasional reports appearing in the literature suggesting its usefulness It has been given recently in combination with glucose

Sakel has advocated the use of insulin in combination with glucose and insulin in combination with barbital sedation scopolomine and digitalis in the management of the withdrawal symptoms Fifteen to 20 units of insulin are given 3 or 4 times daily either with or without glucose as soon as the acute withdrawal symptoms appear The induced hypoglycemic state is thought to stabilize the disturbed balance in the vegetative nervous system but Sakel also has used ergotamine and choline where the parasympathetic system seemed greatly disturbed during withdrawal Sakel reports that from the second day of the treatment there was improvement in appetite in general comfort and in body tone and that the extremely distressing gastrointestinal symptoms ordinarily present during the acute stages were almost entirely absent

Various other supposedly specific drugs or drug combinations have been strongly advocated among the most prominent of which have been narcosan and rossium The Mayor's Committee on Drug Addiction of New York City reported after a study of narcosan that the substance said to be a solution of lipoids together with non specific proteins and water soluble vitamins was not beneficial but increased all of the

sparingly Ten to 15 c c of paraldehyde can be given in olive oil by rectum once or twice daily or sodium bromide can be given in doses of 2 gm (gr 30) two or three times daily in combination with 2 gm (gr 30) of sodium bicarbonate

While no specific benefit has been claimed for the vitamin B compounds in the management of the acute withdrawal symptoms yet the general benefits of vitamin B administration are obvious Vitamin B complex can be given orally in the form of a syrup or in capsules or can be given intramuscularly Thiamin chloride is thought to have some value in those cases where neuritic pains are severe The dose does not need to exceed 50 mgm by intramuscular injection twice daily

Psychotherapy —Since the addict is an obviously emotionally sick individual and since his addiction represents an attempt to overcome his inability to adapt himself in a world of reality the whole reconstructive phase of the treatment hinges upon the success of the psychological rehabilitation The addict suffers fundamentally from too great a discrepancy between ideals and their fulfillment and the individual seeks escape by taking a drug which creates at least temporarily a feeling of adequacy of superiority and an amazing fulfillment of his desire for elation It is a transient state of exaltation which simultaneously restores his infantile self regard and character with erotic satisfaction It is this state which he seeks to produce again and again by the use of the narcotic It is obvious that if the faulty preaddiction character is to remain unchanged after the withdrawal cure it will give rise soon again to the same feelings of inadequacy the same desire to escape into pleasant fantasy and therefore return to the drug will be almost inevitable Psychotherapy either superficial in the form of reeducation or deep in the form of psychoanalysis must be begun immediately after the withdrawal stage of treatment It is essential that no matter how long the psychotherapeutic program the patient must remain in an institution until such time as he has achieved a state of sufficient emotional maturity and stability to warrant a temporary trial outside Since addiction appears to have a progressively degenerative course it is essential that the therapist evaluate the degree of deterioration before undertaking the psychotherapeutic program If the individual's capacity is so impaired that he is unable to endure conflict painful tension states or the stress of living in a world of reality without recourse to the narcotic his outlook even with extensive psychotherapy is not good Not only is this phase of internal psychic readjustment important but the adjustment or correction of insufferable external conditions must proceed also as a part of the rehabilitation Some efforts at family reapproachment is required in most instances A

codeine and morphine withdrawal the morphine was withdrawn rapidly in a four day period but codeine was given in doses of 0 3 gm (gr 5) three times daily alternating with the injections of morphine On the fifth day 0 3 gm (gr 5) doses of codeine were given every four hours and no morphine was given The dose of codeine was decreased gradually until on the 7th and last day of the treatment of a total of 0 4 gm (gr 6) of codeine in 24 hours was given There was little suffering under the 7 day codeine morphine withdrawal and still less under the 14 day morphine withdrawal than in any other method It has been found how ever, that prolongation of the treatment beyond these limits produced some difficulties because while the degree of suffering was less intense it was more prolonged and more difficult to endure The Mayor s Com mittee on Drug Addiction reports that patients suffered less under a rapid withdrawal than under any other form of treatment

Sometimes addicts refrain from undertaking treatment because they fear that they are going to suffer far more than they actually do It is wise and very helpful to give them reassurances on this score and to explain carefully to them that the medical method of treatment even though the withdrawal must be accomplished within a short period never theless can be managed with a minimum of suffering It is sometimes desirable to stabilize all patients with strongly established habits and some of those with the more weakly established addiction on a few grains of morphine a day until they get used to the environment develop confi dence in the physician and have a feeling of assurance that their treat ment will not be brutally managed

Hydrotherapy is very helpful and prolonged tepid baths may be given two or three times a day The sedative action of the prolonged baths is especially valuable since it substitutes so satisfactorily for drug sedation

In cases where the gastrointestinal symptoms are of such severity that vomiting is constant and prevents the patient from taking anything into the stomach 5 per cent intravenous glucose is given two or three times a day in doses of 1 000 c c If the gastrointestinal distress is great and there is a degree of debilitation hypertonic glucose solutions 25 or 50 per cent may be given in doses of 25 to 50 c c This occasionally has a very helpful effect on the restlessness Occasionally the obstinate consti pation will have to be treated by large frequent enemas and colonic irri gations In all cases where constipation is severe saline laxatives or cathartics should be given It is well to avoid excessive purgation Diarrhea occurs sometimes and should be treated by bismuth subcarbon ate in proper dosage If restlessness is extreme, or if there is violent hallucinosis and delirium non narcotic sedative drugs may be given

alcoholic indulgence seems to build up their resistance to the alcoholic intoxication There is undoubtedly some degree of tolerance since there has been reported in the literature that patients may find it necessary to take increasing amounts to obtain the stimulation and have refused to give up the drug when the danger of addiction was called to their attention It is not believed that addiction in the true sense is a likelihood however any more than addiction to coffee In the writer s experience alcoholics during periods of abstinence turn to excessive use of coffee often taking 18 to 20 cups daily or they may employ large quantities of coffee to sober up quickly following a spree Attempts have been made to make the alcoholic individual give up his excessive use of coffee but he refuses to do so on the grounds that he has a constant need for that much stimulation This question therefore of a continuing need for a stimulative drug for physical or psychological reasons is one which is very confusing in attempting to evaluate whether or not true drug addiction is present

German writers recently have called attention to the danger of addiction in *pervitin* which is a benzedrine derivative having almost identical physiological and psychological action

One of the factors which would tend to militate against addiction is the unpleasant effect of continuous benzedrine stimulation Some patients in whom benzedrine has been prescribed in large doses object to taking it because of the disagreeable state of nervous tension and jitters which it produces A few articles have appeared recently calling attention to its danger when used by school and college students who take it in order to sharpen their minds at the time of examinations or in order to stay awake during study and preparation for end of the year examinations Some definite toxic reactions have occurred and collapse has been reported It is also probable that in certain unstable states among psychoneurotics or among hypomanic personalities the drug has precipitated the appearance of acute episodes of excitement which may resemble acute mania The drug should be prescribed with caution in elderly persons because of its possible production of anginoid symptoms particularly in persons who have had previous attacks of angina Occasionally during its medical use persistent insomnia is induced which subsides quickly after the drug is withdrawn The predominant symptoms of overdose are tachycardia sweating feelings of chilliness tremors flushing dryness of the mouth moderate blood pressure rise dilation of the pupils and extreme restlessness and nervous tension emotional instability bouts of laughing and crying and persistent insomnia The antidote is phenobarbital or one of the other barbituric acid derivatives

degree of insight and a helpful attitude should be established in the family to which the addict returns As in other psychiatric illnesses it may be necessary to correct occupational maladjustments or to teach new skills in order that the individual may arrive at some degree of occupational and economic stability

Morphine Substitute — Climenko Batterman Andrews and Himmelsbach have just made a report on the development of a new non habit forming substitute for morphine The new drug is a synthetic preparation chemically described as 1 methyl 4 phenyl piperidine 4 carbonic acid ethyl ester and named for practical usage demerol Favorable results are reported from the first trial of demerol on nearly 1 000 human cases without any toxic effect It may be given orally or parenterally but not intravenously It is slightly less effective than morphine but its non toxicity makes it possible to give larger doses producing an analgesic effect lasting four to five hours The place of this drug in the treatment of morphine addicts is of course, unsettled but it seems to offer an answer to the long search conducted by a great number of scientists for a non addicting substitute for morphine and other active alkaloids of opium In a group of addicts treated in the United States Public Health Service hospitals the painful withdrawal period was definitely mitigated by its use and when recovered addicts were given demerol they did not develop addiction symptoms such as tolerance habituation and dependence

Drugs with Variable or Questionable Addictive Properties

Benzedrine

Benzedrine amphetamine sulphate is a very useful new drug possessing remarkable stimulative and euphoria producing properties Its action is through the stimulation of the postganglionic fibers of the sympathetic Its chief use is in the relief of the pathological sleep syndrome of narcolepsy the depressive states postencephalitic parkinsonism and alcoholic states where its stimulating and euphoric characteristics are of special value Its production of gastrointestinal atonia results in diminution of appetite and this action probably accounts for its occasional use in bringing about weight reduction The question of its addictive liability still is unanswered although any euphoria producing drug has addictive possibilities It has been misused by alcoholics who find that they can indulge in excessive drinking with assurance of quickly sobering up the following day by the use of a few benzedrine tablets Other alcoholics have found that a few benzedrine tablets taken during

by tannic acid solution is recommended If the toxic reaction has been severe and if respiration fails the respirator may be necessary In general the acute excited episodes should be managed by hydrotherapy in the form of prolonged tub baths or wet packs and the increase of elimination by means of purgation

Bromides

There are many habitual users of bromides among the ranks of the neurotics and maladjusted and those who suffer from chronic headache neuritis and neuralgia Bromides should never be prescribed indiscriminately in nervous and mental disorders and this is particularly true in the senile and arteriosclerotic types inasmuch as their ability to metabolize and excrete the drug is greatly reduced The drug is cumulative in effect and toxic stimulation may be reached quickly It is doubtful if there is any true addiction to bromides although constant and excessive dependence on the drug is not at all uncommon It can be argued that there is a certain degree of habituation since withdrawal symptoms do occur

The amount of bromide which can be taken without danger of delirium or toxic psychosis is a variable matter depending on many factors including especially the condition of the arteries the efficiency of the renal mechanism the salt content of the diet and personality idiosyncrasies There seems to be a definite relation between the production of delirium and the blood bromide level While the drug is being administered toxic reactions may occur at a blood level of about 250 to 300 mgm per cent saturation in the serum The symptoms however may persist during treatment until after the level has dropped below 75 mgm per cent Muncie states that the internal economy of the cell is influenced tardily by the progressive accumulation of bromide and likewise tardily gives up its load when excretion in the urine and in the perspiration exceeds the intake

The symptoms of bromide intoxication usually develop gradually but may appear suddenly after weeks of apparent satisfactory response to the drug Fatigue loss of energy somnolence hallucinations and delusions and sometimes acute maniacal reactions are the common manifestations It must be remembered that the so called typical bromide rash often does not appear at all or may appear early in the course of the bromide use and then disappear Neurological signs are loss of pharyngeal reflexes loss of abdominal reflexes weakness unsteady gait dizziness headache dysarthyria tremors and sluggish pupils The pulse

Mariahuana

Mariahuana is the name given in the Americas to the Arabic hashish an intoxicant obtained from the tops and sprouts of the hemp plant The drug may be taken orally but in this country is used most commonly in cigarettes called reefers It induces certain characteristic sensations and reactions It is doubtful if mariahuana is a true habit forming drug or that it produces addiction in the same sense as the opium derivatives since tolerance is achieved only to a very slight degree and there is no demonstrable withdrawal reaction Walter Bromberg believes that mariahuana is a sensual addiction in the service of the hedonistic elements of the personality

The physiological effects of cannabis intoxication are a distortion of time perception and reality feeling a disturbance of consciousness with disorders of memory and retention There is also a change in subjective evaluation of perception of visual tactile proprioceptive and auditory experiences The characteristic behavior reaction is that of an elevation of spirits with sudden boisterous uncontrolled outbursts and moderate impulsiveness The chief danger of the drug lies in the release of aggressive antisocial and sexual drives Bromberg states that the word assassin which means hashish eater owes its connotation to the cruelty practiced by the users of the drug in the Orient The word amuck and hashish are synonymous terms in the Malayan language and natives under the influence of the drug are said to run amuck The mental effects differ in different races and personality types In America Bromberg says that the drug appears to predispose to crime only when it is used by psychopathic types in whom the drug allows the emergence of aggressive sexual or violent tendencies

Often the mariahuana psychosis is imposed upon basic mental abnormalities such as schizophrenia The use of the drug therefore may coincide with the appearance of functional psychotic manifestations In the acute intoxication no permanent ill effects are observed although certain toxic reactions lasting from weeks to months have been reported in some cases

The first experiences with cannabis indica taken orally or by smoking may produce acute collapse but fatal reactions are not known If collapse occurs the treatment should consist of an ice cap to the head stimulation of circulation with caffeine or strychnine the application of external heat to the body and oxygen inhalation If the drug has been taken by mouth evacuation of the stomach and precipitation of the drug

Paraldehyde

Addiction to paraldehyde has been reported but is extremely uncommon Its addictive properties are only slight and it is likely that almost all cases are the result of the patient s experience with paraldehyde during an alcoholic psychosis The drug is useful in the treatment of delirium tremens alcoholic hallucinosis etc and self administration may be resorted to by the alcoholic if he fears himself approaching another acute alcoholic reaction The drug is a liquid somewhat related to ether and has a peculiar pungent odor It is excreted through the lungs and kidneys and the paraldehyde addict is detected quickly by the characteristic odor on his breath The toxicity is low and consequently large doses may be taken before the effect is felt Collapse then may occur suddenly and dangerous delirium may follow its long continued use

Treatment — Treatment calls for immediate withdrawal of the drug Abrupt withdrawal rarely is accompanied by any troublesome symptoms but delirium tremens and epileptic convulsive attacks have been reported If gradual withdrawal is employed moderate use of other sedatives may be necessary to avoid the precipitation of delirium tremens

Barbiturates

The barbituric acid derivatives are not specifically addictive drugs although like many of the sedative substances their continued use may create a sense of abnormal dependence in the unstable individual Barbital formerly known as veronal intoxication is perhaps the most common form of addiction and this comes about in most cases because of persistent insomnia for which the patient has required larger and larger doses of the substance One of its actions which tends to minimize its addiction risk is the rather troublesome hangover which follows the use of large doses This is characterized by mental confusion and depression and occasionally dizziness and incoordination The danger is that barbital being a cumulative drug will reach such proportions that the individual loses contact with reality and loses control of his inhibitory faculties In chronic barbital use the neurological symptoms of nystagmus slurring speech unsteady gait etc may resemble multiple sclerosis There is however a scarlatinal rash usually present which creates a mild burning itching sensation

Addictions to the other members of the barbiturate group can occur in neurotic individuals Sulfanol and trional drugs much like phenobarbital

may be rapid and the blood pressure tends to be low Strecker and Ebaugh recommend the routine use of the Wuth comparator for determining the bromide content of the blood serum This is a relatively simple technique and is of great diagnostic value These authors state that in 1 000 hospital admissions 7 7 per cent showed some degree of bromide intoxication and that 42 per cent of these cases were given the drug on prescription by their physicians in amounts sufficient to produce toxemia

In cases of longstanding severe bromide delirium there may be profound confusion multiform delusions and hallucinations with reactions of intense fear and disorientation in all spheres The breath may have a sweetish fetid odor the tongue is covered with a thick brown fur and there may be marked constipation and occasional retention of urine The skin lesions may be so severe that there appear large sloughing abscesses *Sexual functions are depressed* and *menstrual irregularities* are common The mental picture may resemble closely that of general paresis

The biochemical changes are relatively simple and amount almost solely to the replacement of chlorides in the body by bromides The withdrawal of chloride salts from the gastric secretions and the withdrawal by the bromide salts of fluid from the mucous membranes explain a good deal of the gastro intestinal disturbance Other factors of course are the depression of motility in the gastrointestinal system Muncie states that there is a correlation between the blood bromide level and the degree of replacement of blood chlorides For instance 350 mgm per cent bromide saturation in the serum represents approximately 35 per cent total replacement of blood chlorides (For further discussion of chronic bromide intoxication see Vol IV Chapt XIX–E of Oxford Medicine)

Treatment — Abrupt withdrawal is inadvisable in some cases because of the possibility of precipitating an acute maniacal episode or other excited psychotic reactions The key to the therapy lies in the reestablishment of the chloride balance and the gradual removal of the bromide in the blood stream Ten grams of sodium chloride should be given by mouth daily and 3 000 to 4 000 c c of normal salt solution can be given intravenously to speed the excretion If collapse occurs external heat should be applied to the body Stimulation by caffeine strychnine or oxygen may be given in acute stupors It is permissible to give one of the less toxic barbiturates in the presence of severe excitement Hydrotherapy in the form of continuous tubs and wet packs will serve also to reduce the excitement

solution Oxygen or carbon dioxide inhalations may be given if respiration begins to fail or if complete respiratory collapse occurs artificial respiration or placing the patient in a respirator may be necessary The head should be lowered external heat should be applied if the extremities are cold and stimulants such as caffeine or strychnine may be given intramuscularly or ouabain or strophanthin intravenously Caffeine can be given in combination with sodium benzoate in doses of 0 5 gm (gr 7½) intramuscularly or intravenously Strychnine sulfate can be given hypodermically in doses of 2 2 mgm (gr 1/30) repeated after two or more hours Ouabain is obtainable in 2 c c ampoules each containing 0 5 mgm (gr 1/128) of ouabain Strophanthin is a U S Pharmacopoeia preparation easily soluble in water available in tablet form both should be used cautiously preferably not repeated within 24 hours Ouabain is more toxic than strophanthin and 0 5 mgm each 24 hours rarely should be exceeded Similarly the dose of strophanthin should not exceed 1 0 mgm in 24 hours Both are very irritant if they get into the subcutaneous tissues hence they are for intravenous use

Ether is dangerous because it produces rapid deterioration of kidney liver and the heart muscle Abrupt withdrawal in the chronic cases is the best method of treatment and careful attention must be given to supportive measures if collapse occurs

Chloroform

Addiction to chloroform is essentially the same as addiction to ether and the management is identical

Psychoses due to Sulfanilamide

Widespread use of sulfonamide drugs has produced an occasional case of toxic psychosis In no sense can sulfanilamide be considered an addictive drug Its use in large doses particularly in the minor infectious illnesses is to be deprecated because of the occasional neurovascular consequences Toller reports that patients with psychoses due to sulfanilamide are admitted occasionally to state hospitals for mental disease The psychosis usually is marked by overactivity restlessness occasional violence resistiveness hazy delirium with rambling irrational talk The delusions not uncommonly will take the form of paranoid or depressive trends In one case treated by Toller the first mental symptoms were mild elation and excitement followed later by restless noisy delirium Five days after withdrawal of the drug the mental confusion began to

and barbital in their actions have been reported as having moderately strong addiction liability

If large doses of barbiturates have been taken with suicidal intent or by accident collapse and deep stupor occur Prompt evacuation of the stomach is essential and magnesium sulphate in large amounts should be given by stomach tube Picrotoxin has proved very helpful and may be given in doses of 10 mgm (gr 1/6) intramuscularly or intravenously at intervals of 30 minutes until signs of adequate stimulation have been observed In milder states of barbiturate stupor ephedrine sulphate intramuscularly or intravenously may be given The third day is the critical period in the acute poisonings and generous use of stimulants may be necessary at this time The respirator should be used if medullary depression is severe There is danger of bronchial pneumonia and pulmonary edema in cases of severe poisoning

Chloral Hydrate

Addiction to chloral hydrate has been reported although it is undoubtedly extremely rare Its action is predominantly that of cortical depression and its excessive use produces profound sleep or deep stuporous unconsciousness Long continued use is dangerous because of the damage to the liver and kidney If an excessive dose has been taken either accidentally or with suicidal intent severe collapse with profound stupor may occur The stomach should be evacuated intravenous picrotoxin should be given in 10 to 20 mgm (gr 1/6 to 1/3) doses and external heat and artificial respiration or the respirator may be needed

Ether

Addiction to ether is rare and is said to occur mainly among nurses and anesthetists The psychic effect is that of euphoria and it may produce excited episodes There is of course a subsequent reaction which is severe and marked by profound depression and malaise This discomfort leads to its recurrent use During the prohibition era it was not rare to encounter in the alcoholic wards a curious intoxication caused by the drinking of beer fortified by small amounts of ether The reaction was one of acute collapse followed by profound stupor and delirium The customary use of ether is of course by inhalation and the addict usually takes only sufficient to give the feeling of exhilaration and elation If ether is taken into the stomach the immediate treatment should be evacuation of the stomach followed by lavage with sodium bicarbonate

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subside and at the end of a week the mental symptoms had disappeared entirely A review of the literature shows that the mental symptom occur most commonly in persons of unstable emotional make up

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CHAPTER XXXVIII

DISORDERS OF SLEEP

By PERCY SAUNDERS

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Disorders of sleep may be arranged under three headings deficiency of sleep or insomnia excess of sleep or somnolence and unnatural sleep or sleep disturbed by dreams nightmares somnambulism and kindred phenomena

The normal amount of sleep varies very much in different individuals and depends on the age of the patient on personal idiosyncrasy and also on the quality and soundness of the sleep itself Infants normally sleep twenty hours or more out of the twenty four as the child grows older this amount gradually becomes less but throughout childhood ten twelve or even fourteen hours is a natural amount The ordinary adult requires seven or eight and in some cases nine or more hours a night although five or six hours is sufficient for some people eight hours is usually regarded as about the average After the age of fifty years men and women frequently sleep for shorter periods but often old people require more sleep than they did in their earlier years

INSOMNIA

In certain forms of insomnia the patient is abnormally wakeful and unable to sleep sufficiently his sleep is diminished in quantity below his usual or average amount In other forms sleep is broken and restless the patient tosses about or wakes frequently and finds it difficult or impossible to get to sleep again Or it may be that the quality of sleep is merely indifferent and unrefreshing One or other of these features that is wakefulness dis

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headaches and neuralgia as well as in acute organic diseases and surgical conditions of all kinds Unpleasant bodily and visceral sensations as the irritation due to teething or the presence of worms in infants and children the palpitations of heart disease distention of the stomach indigestion due to gastric and intestinal derangements constipation or a loaded condition of the colon in old people may lead to disturbed sleep or prevent it altogether The general discomfort of acute febrile conditions the dyspnea and cough of respiratory and cardiac affections the vomiting and thirst of abdominal disease the nocturnal frequency of micturition in chronic nephritis or irritability of the bladder the involuntary spasmodic movements of the legs in paraplegia the tinnitus of aural vertigo and otosclerosis and many other such physical causes are responsible for much difficulty in sleeping *In these conditions abnormal afferent impressions impinge on* consciousness and prevent the dulling of the higher cerebral activity that accompanies sleep

In intoxication by various drugs as alcohol cocain and henbane in opium taking and various drug habits in acute infections like typhoid and other fevers in cachectic states such as pernicious anemia and malignant disease in exhaustion in uremia and in various constitutional and metabolic diseases the action of a poison or toxin on the central nervous system is the cause of sleeplessness In many of these states the transition between wakefulness and delirium on the one hand and drowsiness and stupor on the other is slight and the same cause may be responsible now for the one set of symptoms now for the other Anemia of the brain due to hemorrhage shock heart failure and cerebral arteriosclerosis may also produce insomnia That of old age is frequently associated with disease of the cerebral vessels

In certain organic or functional diseases of the nervous system interference with sleep is a common symptom in primary cerebral infective and toxic conditions as encephalitis and meningitis the excitability of the brain may be a bar to sleep This may be the cause also of the insomnia that follows severe head injuries and concussions In general paresis and sometimes in cerebral syphilitic disease the diurnal irritability and excitability are frequently accompanied by sleeplessness at night In various insanities too insomnia is a frequent and persistent symptom it accompanies the cerebral excitability of acute mania and the depressive irritability of melancholia and the exhaustion psychoses In neurasthenia and psychasthenia inability to sleep is often the dominant feature insomnia is in fact one of the most common symptoms of neurasthenia It is less frequent in hysteria

In neurasthenia psychasthenia and the exhaustion psychoses and in certain forms of chronic persistent insomnia occurring independently of

turbed sleep or unrefreshing sleep, may be the characteristic symptom in different cases

Insomnia may be a slight and occasional condition due to some temporary disturbance or it may be a chronic protracted condition of severe and persistent loss of sleep night after night, so that the habit of sleep becomes more or less lost In some cases it occurs chiefly at certain periods of the night in others the whole night through Thus some patients find a difficulty in getting off to sleep but then sleep more or less naturally throughout the rest of the night others find it not only difficult to get to sleep but wake repeatedly others go to sleep on retiring but wake after a few hours and then cannot sleep again at all or keep waking every hour or so throughout the night while others wake habitually in the early hours of the morning and lie awake for several hours till it is time to get up No specific causation to any extent attaches to these different varieties of sleeplessness and broken sleep Severe pain for instance may cause interrupted fitful sleep for longer or shorter periods or prevent sleep altogether Older patients with arteriosclerosis are prone to sleep in the early part of the night and lie awake in the early morning while patients with neurasthenic insomnia often find it difficult to get to sleep, but are drowsy and disinclined to wake in the morning Neurasthenia however, may be responsible for all varieties of disturbed sleep and sleeplessness

Among the causes of slighter insomnia are various disturbances in the environment and mode of life of the patient Some of these may be trifling in character Uncongenial surroundings any unaccustomed noise or light at night an uncomfortable bed the weight of the bed clothes or a badly ventilated room may produce sleeplessness in susceptible persons Atmospheric conditions and change of climate may lead also to temporary disturbance of sleep Interference with the ordinary hours and habits of sleep too often produces temporary insomnia nurses and others who work at night frequently experience a difficulty in sleeping by day or on changing back to day duty sometimes suffer from more or less insomnia at night So strong is the force of habit, indeed that people who have grown accustomed to some special noise at night may in its absence be unable to sleep for a time Late dinners or suppers or a heavy meal before bedtime are commonly causes of insomnia in those unaccustomed to them alcoholic drinks and tea or coffee in excess as well as mental and physical fatigue frequently prevent or retard normal sleep the student who devotes the late hours of the evening to strenuous work may be unable to sleep when he retires to bed

Pain due to injuries or disease is one of the most common and important causes of insomnia and bodily pain and sleeplessness frequently go hand in hand as common symptoms in many dissimilar conditions, in ordinary

should be in a quiet part of the house and should be comfortable not too soft the clothes light in weight the temperature of the room moderate *and the room properly ventilated The hours for retiring should be regular* no heavy or indigestible food should be taken for some time before going to bed and coffee tea and alcoholic stimulants should be avoided as a rule although often a hot drink of milk bovril or weak whiskey just before retiring tends to promote sleep If mental factors are responsible for the insomnia careful enquiries should be made into any causes for worry or anxiety on the part of the patient and steps should be taken to have these corrected as far as possible for as long as the mental or emotional causes of sleeplessness still exist treatment of the condition is far from hopeful Overwork and fatigue any excitement or work in the evening and particularly strenuous mental work just before going to bed should be carefully avoided

In those cases in which bodily derangements are present such as indigestion in gouty patients constipation in old people eye strain symptoms of arteriosclerosis or high blood pressure or any other concurrent condition that might be a source of irritation attention must be directed in the first place to the treatment of such conditions In those cases too where the insomnia is a symptom in some more serious acute or chronic disease and the patient is already confined to bed its treatment is that of the condition with which it is associated although frequently the symptomatic relief of the sleeplessness is an important part of the treatment as a whole Pain causing insomnia requires treatment by various analgesics If the discomfort associated with acute febrile and delirious conditions be relieved by sponging the patient may be able to get to sleep Careful nursing is essential for attention to such matters as the evacuations of the bladder and bowels and the general comfort of the patient are of primary importance and often more effective than the administration of drugs In chronic illnesses a different bedroom for the day and night may be a great help The personality of the nurse is important too particularly for neurasthenic patients as a cheerful and competent attendant can not only allay the petty worries and anxieties that disturb rest but can also inspire the confidence that is necessary to ensure good sleep

Patients who are not confined to bed usually benefit by taking during the day some outdoor physical exercise which tends to promote a feeling of fatigue and conduces to sleep but overfatigue must be avoided A moderate *amount of relaxation and amusement and change of occupation are* advantageous if the patient is well enough In some neurasthenic cases and in those due to overwork a change of surroundings is beneficial High altitudes should be avoided as a rule and it must be remembered that some patients do not sleep well at the seaside in others sea voyages are of great value

Physical therapy is in many cases one of the most potent modes of treatment A hot bath at bedtime followed by gentle massage often helps to give sleep but the masseur or masseuse must be carefully chosen as his or her personality may be the determining factor Music of a monotonous and not too loud character or gentle motion may be of help Some patients find a monotonous uninteresting book that does not tax the attention of value others adopt various devices such as counting or solving a puzzle The latter methods however are of very dubious worth and frequently of no avail or they may be definitely harmful The static breeze before bedtime is helpful in relieving the headache that frequently accompanies insomnia and various other electrical or mechano therapeutic measures are useful, especially in neurasthenic cases

The medicinal treatment of insomnia should be considered very carefully in every case Powerful hypnotic drugs should be used with caution and discretion and should be dispensed with if it is possible to obtain sleep by other methods The proper use of digitalis in heart disease of asthmatic remedies in asthma of strychnin and stimulants in cases of overwork fatigue and exhaustion of various carminatives and other drugs in dyspepsia of laxatives in constipation, as well as analgesic drugs for the relief of pain and discomfort often render the use of hypnotics unnecessary Sedatives can be more safely employed the simplest and least harmful of these are the bromides of sodium and potassium which are particularly useful in cases of insomnia associated with mental restlessness or due to emotional or mental causes They are best administered in small doses during the day with a larger dose at night for instance ten grains (0 6 gm) of sodium bromide three times a day with twenty grains (1 3 gms) at bedtime or the last dose may be advantageously combined with ten grains (0 6 gm) of acetyl salicylic acid (aspirin) Frequently perseverance with this treatment together with other physical measures is quite sufficient after the habit of sleep is restored the drugs can be gradually withdrawn

It may be necessary however, to combine with these drugs other more powerful ones for a short period three to five grains (0 2 to 0 3 gm) of veronal may be added to the aspirin at night for several nights in succession and then gradually withdrawn The combination of aspirin with veronal enables a smaller dose of the latter to be used with good effect It should be prescribed as barbitone rather than veronal because of the notoriety attaching to the latter term It must be remembered that even moderate doses of these powerful hypnotics may produce depressing effects the next day in some patients and their continued use must be avoided for this reason and owing to their liability to engender a habit Dial medinal and other similar drugs may be used for a short time but should be reduced or discontinued as soon as the habit of sleeplessness is broken

Various other hypnotics that are used occasionally may be mentioned briefly Sulphonal and trional which are less frequently employed now than a few years ago are comparatively safe in small doses although somewhat depressing They may be advantageously given together the sulphonal continuing the effects begun by the trional or they may be combined with bromides Chloral hydrate is not of great value in cases of protracted insomnia although useful as an occasional drug it is comparatively safe even in heart disease notwithstanding the prejudice to the contrary Some of the drugs allied to chloral as chloretone and chloralamide are useful in insomnia associated with great nervous restlessness as for example in severe chorea but as they are apt to be depressing they must be employed with care Butyl chloral hydrate is frequently combined with sumbul in the treatment of trigeminal neuralgia and its sleeplessness Paraldehyde is a very useful drug in insomnia associated with heart affections and various functional conditions Its disagreeable smell and taste are useful in preventing the formation of a habit some patients who take it night after night experience no depressing effects the next day

In the insomnia due to pain bromides and the simpler sedatives are not of much value unless the pain is slight or its effects are being kept up mainly by the patient s mental condition when it is real and severe opium and its derivatives are necessary and in many cases they are the only drugs likely to be effectual They may be given in the form of Dover s powder in ten grain doses (0 6 gm) tincture of opium liquor sedativus or compound tincture of chloroform or morphin by mouth or hypodermically or as omnopon or heroin In the severe pain and insomnia of acute illness it is often better to use morphin hypodermically than to temporize with less certain methods In chronic illness however where the pain and sleeplessness are likely to continue it is unwise to have recourse to opiates until it is absolutely necessary since the patient quickly becomes accustomed to them and as the dose is increased its harmful effects soon become apparent on the appetite digestion and bowels Omnopon heroin and opium by the mouth instead of hypodermically are sometimes more useful than morphin As a rule it is well to begin with combinations of less potent drugs as the coal tar preparations and to use different drugs from time to time

In the insomnia of mental disease and delirium hyoscin is extremely valuable it should be administered hypodermically and at first only small doses should be used lest the patient display a dangerous idiosyncrasy Morphia often acts as a charm in cases of melancholia with restlessness and insomnia In the case of both these drugs however the injections may be combined or alternated with doses of sulphonal trional or veronal

Some patients with hysterical and neurasthenic sleeplessness show great resistance to drugs even large injections of morphia may have no effect

Physical therapy is in many cases one of the most potent modes of treatment A hot bath at bedtime followed by gentle massage often helps to give sleep, but the masseur or masseuse must be carefully chosen as his or her personality may be the determining factor Music of a monotonous and not too loud character or gentle motion may be of help Some patients find a monotonous uninteresting book that does not tax the attention of value others adopt various devices such as counting or solving a puzzle The latter methods, however are of very dubious worth and frequently of no avail or they may be definitely harmful The static breeze before bedtime is helpful in relieving the headache that frequently accompanies insomnia and various other electrical or mechano therapeutic measures are useful, especially in neurasthenic cases

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logical states In some of the psychoses the patient may spend a great deal of his time in sleep and individuals of dull mentality but otherwise normal may contract the habit of sleeping to excess Older patients with arterio sclerosis frequently dose very readily during the day

Excessive sleep occurs also in various neuroses Narcolepsy is a state of profound sleep into which hysterical subjects are liable to fall suddenly it may last from a few minutes to several hours and usually comes on with little or no warning and tends to recur at varying intervals In other respects the patient is quite healthy and the examination of the nervous system reveals no physical disease to account for it Some of these cases are closely related to epilepsy and the condition may sometimes be an epileptic equivalent but in others it can be regarded only as an hysterical phenomenon Catalepsy and hysterical trances belong to the same category Deep sleep usually follows an epileptic fit also and it may be prolonged for days when the fits are frequent or when status epilepticus develops In other cases of epilepsy a sleepy or dreamy state may constitute the aura of an attack

Drowsiness may be a premonitory phase of the unconsciousness stupor or coma that develops in various organic diseases In certain diseases involving the brain such as cerebral tumors abscesses gummata and tuberculomata drowsiness and mental hebetude are common symptoms In encephalitis and meningitis of different forms and in cerebral syphilis and acute disseminated sclerosis drowsiness often supervenes in one form of encephalitis it is such a prominent feature that it has given to the disease the name encephalitis lethargica Drowsiness occurs also in general toxic conditions as uremia and diabetes in some chronic auto or hetero genetic intoxications in profound anemia in general infectious and febrile states such as influenza and pneumonia and in poisoning by such drugs as alcohol morphin belladonna hashish and chloral Drowsiness is also the chief clinical feature of trypanosomiasis or sleeping sickness Somnolence occurs too in certain affections of the ductless glands as in Frohlich s syndrome which is due to pituitary disease and in myxedema A tendency to excessive sleep is often present in obesity

In these different conditions drowsiness is but a symptom and its treat ment is embraced in that of the pathological condition with which it is associated

Dreams and Kindred Phenomena

Sleep may be disturbed by dreams by night terror nightmares som nambulism and somniloquy

Dreams occur so readily and pass so unnoticed that unless they become

in hysterical insomnia though the condition may yield to simpler measures combined with appropriate forms of pyschotherapy It is in such cases that suggestion is of such great value in fact the results obtained by the administration of drugs in some of these cases may be due to it rather than to the pharmaceutical action of the drugs Hypnotism too is often effective in such cases and its use is not limited to them as it is sometimes a valuable measure in the treatment of insomnia dependent upon other psychical disorders

When a phobia prevents sleep or a fear or terror complex leads to alarming or distressing dreams that interrupt it the careful investigation of the patient s psychical state and the unravelling of the grounds of his fear may gradually remove it It is in such cases that a rational analysis of the subconscious factors is necessary in order to eradicate the psychical disturbance

The principles in the treatment of insomnia therefore are few but important Powerful hypnotic drugs should be used only for their immediate effect in acute cases or when severe pain is responsible for the sleeplessness In more chronic cases small repeated doses of less depressing drugs as bromides and aspirin should be employed Drugs should be used primarily as an aid to other measures however for insomnia is frequently only a symptom of some disease and then it is best dealt with by treatment of the condition that produces it When the more powerful drugs are necessary they should not be continued long their effect should be carefully watched and as soon as sleep is obtained they should be reduced in dose and gradually withdrawn The great importance of physical and psychical measures should not be forgotten Where mental and psychical factors are responsible for sleeplessness it is impossible to hope for relief from the administration of drugs alone if the overwork or sources of worry or emotional disturbances still exist In such cases it is essential to remove the cause and purge the mind of the obsessions or psychical factors on which the symptoms depend

Somnolence

Somnolence drowsiness or excessive sleepiness may occur as a physiological condition resulting from mental or physical fatigue working in an ill ventilated or overheated room and various other causes A heavy humid atmosphere the unusual quietness of a hot summer s day prolonged exposure to extreme cold as well as monotonous sounds or movements and too long or too continuous mental application to some one subject or to a subject that fails to hold the attention may produce it

A tendency to excessive sleep occurs also as a symptom of many patho-

and objects are often grossly magnified The incidents of dreams as a rule are presented in the shape of pictures or visual hallucinations although auditory and other hallucinations occur also Certain types of dreams tend to recur frequently sensations of *falling* through space for instance are very common and these have been variously and often fantastically explained by psychologists Another feature of dreams is the rapidity and ease with which they are forgotten on waking their lines become blurred in many cases almost at once so that the individual may be quite unable to recall in the day the substance of a vivid dream of the night before In other cases however a dream may be remembered for years or again some particular dream may repeat itself over and over again There is scarcely any dogmatic statement indeed that can be made about dreams without immediate qualification

In some cases the sensations associated with the dreaming state are very vivid and exciting and give rise to night terrors nightmares night pains sleep talking and sleep walking or these may occur apart from any remembered dream although they are obviously related phenomena

Night terrors are states of mental excitement associated with hallucinations they occur most commonly in children between the ages of three and eight years They are frequent in ill health in febrile or digestive disturbances and particularly in nervous imaginative children They are most apt to occur in the early part of the night within an hour or two of going to sleep The child suddenly starts up in bed with a scream and often calls out the name of the object the image of which frightened him or he may try to get out of bed and escape from the room He is obviously in a state of great fear which may not subside for a considerable time despite all efforts made to soothe him During this period he still sees the terrifying vision and may not recognize people about him At length he wakens recognizes those around him then sinks down exhausted and soon goes to sleep The hallucination of robbers a dog or whatever it was is usually remembered by the child next day and may be a source of great depression to him on retiring the next night In many cases the same hallucination repeats itself time after time

Nightmares are conditions of terror associated with unpleasant dreams from which the patient wakes with an overwhelming sense of fear and often with a cry and trembling The contents of the dreams are usually more varied in character than are the hallucinations associated with night terrors and they are not so apt to recur regularly although they may repeat themselves during the same night Nightmares are more often associated with ill health and with digestive disturbances than night terrors and the neurotic element is not such an important factor as in the latter They occur more often in older children than do night terrors and in adults but the distinction

excessive or distressing in character they are regarded as natural phenomena One school of psychologists in fact assumes that all sleep is accompanied by dreaming though no memory of the dreams may persist in the waking state the dream is for them merely the manifestation of the psychical activity that belongs to sleep This hypothesis is impossible of proof or disproof for the memory of the dream is the chief means we have of establishing its existence but from the medical point of view that explanation of dreams and kindred phenomena is best which regards them as due to absence of the usual dulling of consciousness and mental activity that occurs in normal sleep or as evidence that isolated and disconnected parts of the higher cerebral functions remain abnormally active The frequency of dreams in the light sleep just before waking supports this view for that state between sleeping and waking when we are almost conscious of being asleep is most prolific in dreams these often come to a sudden and abrupt end on the intrusion of some external sensation At first this intruding sensation is skilfully woven into the fantastic jumble of the dream and only as it becomes more insistent is it suddenly accepted at its real value

Dreams are due therefore to various external causes or to mental or psychic factors They may arise from external sensory impressions that are not entirely ineffective in sleep or from internal sensory stimuli or from normal or pathological stimuli arising in the different viscera Finally psychic excitations resulting from memories emotional disturbances and overstrain may of themselves be sufficient to start off the dream activity This suggests the importance of the nervous temperament of the patient in predisposing him to dream accounts for the fact that some people dream habitually or much more than others and accounts too for the distressing dreams and night terrors that affect nervous and unstable children, or people who have experienced severe shocks or emotional stresses which have left an indelible impression on the conscious and subconscious level of their minds It accounts also for the fact that to a certain extent dreams may be cultivated and the habit of them acquired

In most cases dreams bear a definite relation to the events of ordinary waking life and are conditioned by the daily happenings and experience of the individual Usually the connection is obvious although the dream may be related to slight and trivial events of the day that have not particularly impressed the individual at the time of their occurrence Sometimes however the connection may not be so obvious or the dream may recall some long forgotten event or experience

The ordinary character of dreams are well known and need not be described in detail Their content is usually incoherent and fantastic as compared with waking experiences and the combinations of events are quite different from the logically governed happenings of waking life while events

then the setting of things before him in their proper light and perspective may be sufficient to purge his mind of the disturbing factor But in other cases the interpretation of intangible incoherent half remembered dreams is very difficult and the enthusiastic interpreter who comes to the task with a preconceived set of symbols whereby he attempts to rationalize the fantastic jumble of the dream must always be on his guard lest he so magnify the importance of his symbols that he lose the guidance of common sense for symbolism is at the best only an hypothesis and any interpretation may be grafted on any symbol

The treatment of night terrors in children is frequently difficult success depends more on the careful management and upbringing of the child than on medicinal measures The child should be placed in as healthy and natural *surroundings as possible he should be carefully persuaded during the day* to lose his terror of the dog or other object which appears in his terrifying hallucinations at night unnatural excitements should be avoided and no attempt should be made to force his education A night light in the bed room frequently stops the terrors When they recur so often that they disturb seriously the child's rest bromides and other sedatives may be given at bedtime

between the two conditions is not sharply drawn and the difference is more or less one of degree Nightmares and to some extent night terrors also may occur after shocks or emotional disturbances and in alcoholism and incipient insanity

In *somniloquy* the patient carries on a conversation of greater or less length during sleep but has no recollection of having done so the next morning It occurs frequently in delirious states

Somnambulism is a rare condition which may occur either by itself or in association with dream The patient otherwise asleep gets out of bed and usually without dressing walks about the house or even out into the street finally coming back to bed again and the next day has no recollection of the event at all During the attack he may carry out various purposeful actions and avoid obstacles in his way with safety although occasionally he may make mistakes and injure himself Frequently he sees only in regard to the events of his dream and therefore may sometimes come to grief by not observing objects around him Somnambulism may occur in childhood in association with febrile illnesses indigestion or other bodily complaints or it may recur frequently in susceptible but otherwise normal children It usually ceases as the child grows older

It may occur also in apparently healthy adults but is most often found in epileptics and in the subjects of chronic alcoholism In epilepsy it may be either a psychical equivalent of a seizure or a manifestation of automatism after either a major or minor attack Sleep walking occurs also in certain psychoses especially in dementia praecox

Treatment

Dreams require treatment only when they become distressing or so frequent as seriously to disturb sleep Any causes of sensory or visceral irritation or of emotional disturbances or overstrain that may be present should be removed All excitement in the evenings and late meals before going to bed should be especially avoided Of drugs the most important are the bromides and these may be employed regularly at bedtime as in the treatment of insomnia Associated organic or functional disease must be treated also Patients in somnambulism should not be roughly wakened but should be gently led back to bed

The study and interpretation of dreams may be of value in the explanation of abnormal behaviour in or of the origin of the psychoneuroses as the psychical activity of the sleeping state may allow some of the jetsam and flotsam of the subconscious which are forgotten or repressed in the waking consciousness to come to the surface The clue may be given by a dream in which the patient lives over again some tragic scene or emotional event

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CHAPTER XXXIX

TETANY

By Samuel B. Grant

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Definition — Tetany is a symptom complex characterized by increased irritability of the neuromuscular apparatus to mechanical and electrical stimuli. The small muscles are affected chiefly and the principal symptoms are involuntary tetanic spasms of the extremities, spasms of the larynx and generalized convulsions. Often there are associated tingling sensations or other paresthesias. Tetany occurs under a large number of different circumstances and usually is associated with some other disorder of the body.

Etiology

Modern knowledge of the physiology of tetany divides its causative factors into two groups, first, tetany associated with a diminution of the total blood calcium, and second, tetany associated with a shift of the acid base equilibrium to the alkaline side. It has been possible to prove or

assume one or the other of these two fundamental abnormalities in all of the various circumstances in which tetany is observed Thus hypocalcemia is found in parathyroprivia infantile tetany tetany of pregnancy and lactation tetany of steatorrhea phosphate tetany and may be assumed in idiopathic tetany Alkalosis is demonstrable in tetany of hyperpnea overdosage with sodium bicarbonate and in gastric tetany

Physiologists have known for many years that a decrease of calcium leads to increased irritability of tissue In 1907 and 1908 Parhon and Urechi and MacCallum and Voegtlin discovered independently that the administration of calcium salts relieved the symptoms of parathyroid tetany and MacCallum and Voegtlin demonstrated that there is a marked diminution of blood calcium in the tetany of parathyroidectomized dogs Greenwald (1924) and later Albright Bauer Ropes and Aub (1929) have presented evidence that the primary effect of parathyroprivia is to diminish renal excretion of phosphorus the consequent retention of phosphate forcing down the concentration of calcium The low blood calcium thus might be secondary to a high renal threshold for phosphorus in parathyroidectomized animals There is considerable evidence that a low phosphorus diet is helpful in the treatment of this type of tetany aiding the effect of high calcium diet in elevating the serum calcium content

Howland and Marriott (1918) found a reduction of the blood calcium in infantile tetany and also discovered that the administration of calcium salts to infants with tetany relieved the symptoms Attempts to prove a disorder of the parathyroid glands in infantile tetany met with failure and it is now accepted generally that infantile tetany is independent of parathyroid gland disease

Studies of vitamin D deficiency have led to the belief that this is a primary factor in the production of the hypocalcemia of infantile tetany with dietary deficiency of calcium as an added factor The same mechanism would explain idiopathic tetany as found among indoor workers under certain conditions to be explained later

The work of Holtz (1931) in isolating a fraction of irradiated ergosterol which has a specific effect in elevating blood calcium is of particular importance in relation to the problem of dietary and vitamin deficiencies as a cause of hypocalcemic tetany The calcinose fraction of irradiated ergosterol is quite independent of the antirachitic factor It has been isolated as dihydrotachysterol and more conveniently named A T 10 This substance is so powerful in its blood calcium elevating effect that toxic symptoms of hypercalcemia are produced easily and it should not be used except under careful control by serum calcium determinations

Hypocalcemia may be found during pregnancy and lactation in steatorrhea and in phosphate tetany for reasons to be explained under these various headings later

Alkalosis very obviously is present in several types of tetany and without any reduction in the total amount of serum calcium In overdosage with sodium bicarbonate alkalie is added to the body more rapidly than it can be excreted or neutralized with a consequent marked increase in the alkalie reserve and an increase in the $\frac{NaHCO_3}{H_2CO}$ ratio in the blood In the tetany associated with persistent vomiting as in pyloric obstruction there is a similar increase in the alkalie reserve presumably due to the fact that gastric hydrochloric acid is lost to the body leaving a relative excess of alkalie The blood chloride is reduced markedly In overbreathing there is an alkalosis due to the washing out of the acid carbon dioxide from the blood leaving a relative excess of alkalie (Grant and Goldman 19 0) The alkalie reserve becomes decreased in forced breathing as a result of mechanisms which tend to balance the amounts of carbonic acid and sodium bicarbonate in the body fluids but it has been demonstrated that there is an actual increase in the alkalinity of the blood and hence a true alkalosis in the tetany of hyperpnea

The tetany of alkalosis is identical with that of hypocalcemia and it is natural that attempts would be made to demonstrate a common mechanism If it could be shown that in alkalosis the amount of calcium in ionized form was reduced drastically although the total blood calcium was normal the problem would be quite simple Since the physiological activity of calcium presumably is due only to that part of its total quantity which is present in the ionized state both alkalosis and hypocalcemia would then cause tetany because of a diminution of ionized calcium in the blood and tissues That this might be the case was suggested by the work of Rona and Takahashi (1913) who showed that the degree of diffusibility of calcium in solution through a membrane impermeable to protein depends upon the concentration of bicarbonate and hydrogen ions present This would seem to prove the case that alkalosis produces tetany by reducing the amount of physiologically active calcium

Against this theory however is the fact that McCanse and Watchorn (1937) found that in the tetany of overbreathing there was a small rise in both the total and in the ultrafiltrable calcium in the serum and no change in the cerebrospinal fluid calcium Cumings and Carmichael (1937) also found the cerebrospinal fluid calcium which has been assumed to represent diffusible calcium unchanged in tetany of hyperpnea McLean and Hastings (1935) studied the conditions affecting the ioniza

tion of calcium by perfusing the isolated frog's heart with various solutions The amplitude of the heart contraction is sensitive to slight changes in calcium ion concentration and the method of study would appear to be quite as pertinent to the question at hand as the estimation of the amount of calcium diffusible through a membrane As a result of their studies McLean and Hastings found that the tetany of alkalosis does not appear to be associated with diminished concentrations of calcium ions in the plasma

Martin (1926) has correlated the tetany of hypocalcemia and of alkalosis upon a possibly different basis than a common diminution of calcium ionization He pointed out that there is evidence that muscle contraction is due to the disruption of lactacidogen into free lactic acid and phosphoric acid and that as shown by Embden (1925) this breakdown is favored by a decrease of hydrogen ion concentration in the surrounding medium Evidently an alkalosis would urge the setting free of lactic acid and phosphoric acid Similarly Lange (1924) showed that diminished calcium concentration favored the breakdown of lactacidogen In either case the process would be accompanied by muscle fiber contraction The signs of latent tetany (Erb Chvostek Trousseau) could be explained by the theory that lactacidogen would be so near the disrupting point that slight nerve stimulation would release the effective acids The small muscles of quick action such as those controlling the larynx face and fingers contain relatively more lactacidogen than larger and slower muscles and this might explain the distribution of the spasm in tetany

HYPOCALCEMIC TETANY

Parathyroid Tetany

This is fully discussed in the chapter on diseases of the parathyroid glands (see Vol III Chapt XV) and need not be considered here other than to mention that Holtz (1931) made an important contribution to the treatment of parathyroid tetany in the use of A T 10 particularly in regard to those cases in which administration of calcium salts and vitamin D fails to control the symptoms and in those which have become resistant to the effects of parathyroid hormone The fraction of irradiated ergosterol isolated as dihydrotachysterol (A T 10) has a powerful effect in elevating serum calcium and is so potent in fact that its use must be controlled by frequent serum calcium determinations in order to prevent the toxic effects of hypercalcemia

Infantile Tetany

Infantile tetany is more common than any of the others and occurs chiefly between the ages of six months and two years In the vast majority of instances signs of rickets are present although usually this is of mild degree and not the markedly deforming type or at least has not reached that stage In those few cases that show no external evidence of rickets it is quite possible that pathological studies would demonstrate the presence of lesions of the disease Both rickets and tetany are much more common and severe in the winter and spring months and both are more common in artificially fed infants although they may occur in those that have been breast fed The tetany may be latent in which case it is recognized only by the presence of certain signs to be described below The active manifestations include carpopedal spasms laryngospasms and generalized convulsions

Latent Tetany

Latent infantile tetany may be entirely without symptoms or may display itself in an undue restlessness irritability and crying The diagnosis in these instances may be made by examining the child for the following signs of tetany (1) *Chvostek s sign* elicited by tapping the side of the face over the course of the facial nerve If tetany is present there will be a swift transient contraction of the muscles about the mouth or eye depending on the branch of the nerve that has been stimulated In infants this sign is pathognomonic but in children over three years old it may be present in the absence of any other evidence of tetany (2) *Trousseau s sign* elicited by compressing the arm above the elbow for from one to three minutes when a typical carpal spasm of tetany will occur (3) *Erb s sign* of electrical hyperexcitability This is determined by measuring the milliamperes of galvanic current necessary to cause a muscular contraction when cathodal and anodal shocks on opening and closing the circuit are applied to a superficial nerve The ulnar nerve usually is used The current for the cathodal opening contraction is the most important Normally more than five milliamperes are required to produce such a contraction in children under five years old In tetany a current of less than five milliamperes will cause a contraction

Less frequently used tests are (1) the *peroneal nerve test* elicited by tapping the leg at its lateral surface just below the head of the fibula which will cause a dorsal flexion and abduction of the foot and (2) the *nerve tension test* elicited by maneuvering the arm or leg to stretch the

tion of calcium by perfusing the isolated frog's heart with various solutions The amplitude of the heart contraction is sensitive to slight changes in calcium ion concentration and the method of study would appear to be quite as pertinent to the question at hand as the estimation of the amount of calcium diffusible through a membrane As a result of their studies McLean and Hastings found that the tetany of alkalosis does not appear to be associated with diminished concentrations of calcium ions in the plasma

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occasionally results in *death*. Some of the infants with active tetany exhibit all three of the major symptoms convulsions carpopedal spasms and laryngospasms and all cases show the signs of tetany listed above

Course and Prognosis

Active tetany may last for from a few days to several weeks occasionally much longer. The symptoms usually will cease spontaneously as summer comes on but may be controlled readily at any time in most cases by *appropriate treatment*. The *prognosis as to life is good because the* laryngospasm rarely is so severe as to cause death and the convulsions usually are not dangerous. Most of the infants show no after-effects in later life although it is said that some of them suffer from nervous manifestations such as enuresis stuttering tic headaches etc

Treatment

The treatment of infantile tetany resolves itself into two parts first the immediate alleviation of the active symptoms such as convulsions and second the correction of the underlying deficiency of *calcium* and vitamin D

In most cases all the active manifestations may be made to disappear in a few days by administering calcium chloride with the feedings 0 5 to 1 0 gram (gr 7½ to 15) four or five times daily. This treatment must be continued for some time or else the symptoms will reappear promptly. Calcium alone will not affect the underlying condition and additional treatment therefore must be directed at the associated rickets. For this purpose vitamins A and D are most valuable preferably in the form of cod liver oil although some of the other fish oils and viosterol may be used also. It is important that this treatment of the underlying vitamin deficiency be persisted in. In all cases a rational diet should be prescribed depending upon the child s age and digestive symptoms. A mixed diet generally is considered to be advantageous. In infants breast milk although not essential would be a distinct advantage

It may be necessary to administer chloroform for the more severe convulsions. For very frequently repeated convulsions or laryngospasms it is wise to use sedatives until the condition is controlled by calcium administration. For this purpose chloralhydrate 0 13 to 0 3 gm (gr 2 to 5) by mouth or by rectum or small doses of morphine hypodermatically are quite valuable. Magnesium sulphate intramuscularly in doses of 0 5 to 1 0 gram (gr 7½ to 15) depending upon the age of the child has been highly recommended

brachial plexus or sciatic nerve which will produce a carpal or pedal spasm

The important laboratory test is the determination of the serum calcium which is reduced drastically, often to 5 or 6 milligrams per cent in tetany Normal blood serum contains 10 to 11 milligrams per cent In rickets uncomplicated by tetany there is only moderate reduction The inorganic phosphorus content of the blood is either within normal limits or reduced as it is in rickets

Active Tetany

Active tetany may become manifest only at the onset of some mild or severe febrile disease which may precipitate a convulsion or the convulsions laryngospasm or carpopedal spasm may appear in a child who was considered well or possibly merely fretful and irritable Tetany is a common cause of convulsions in infancy and undoubtedly is the basis of many of the convulsions formerly attributed to teething weaning or other coincidental occurrences The individual convulsions are similar to those of epilepsy but in epilepsy the attacks usually come on at long intervals and continue into later years whereas in tetany there may be a series of frequent convulsions particularly in the late winter or early spring These disappear as summer comes on, or when appropriate treatment is instituted The above mentioned signs of latent tetany will be present between attacks and serve to differentiate the two diseases

Active tetany may be manifested by attacks of carpal spasm, in which the hands are held in the typical so called obstetrical position with the fingers stiffly flexed and adducted and the wrists flexed The feet often are involved in a similar spasm These attacks may recur at frequent intervals throughout the day each one lasting for from a few minutes to an hour or more or there may be continuous spasms for days at a time the hands and the feet assuming characteristic position whenever no voluntary motions are being carried out The infants often appear to be suffering pain during the attacks In many cases the muscles of the face are partially contracted especially those about the mouth giving the face a peculiar expression The only active manifestation in some infants may be laryngospasm These are attacks of breath holding during which the infant may be cyanotic and finally inspire with a loud crowing sound The attacks may be precipitated by fear anger and other excitement and for this reason are often attributed to wilfulness on the part of the child In severe cases there may be serious and continuous dyspnœa with stridor cyanosis and great distress Spastic apnea

TETANY OF STEATORRHEA

In the chronic diarrheas in which there is excessive loss of fats with the stools hypocalcemia and tetany may develop This is found most frequently in non tropical sprue in adults and in celiac disease in children considered by many to be a form of sprue Blumgart (1923) Holmes and Starr (1929) and Linder and Harris (1930) and others have demonstrated the hypocalcemia in such cases It has been suggested that the calcium may be lost as calcium soaps in the frequent fatty stools but vitamin D deficiency may be the primary cause Osteomalacia the adult form of rickets with decalcification of bones and even spontaneous fractures may occur Snell and Camp (1934) suggested that the vitamin D deficiency might be due to loss of the fat soluble vitamins in the fatty stools They demonstrated in three of seven cases x ray evidence of disease in the upper part of the small intestine the area in which calcium presumably is absorbed and suggested that such disease might be another factor in producing tetany in steatorrhea

Fat restriction in the diet and large doses of irradiated ergosterol have been effective in the treatment Holtz A T 10 would have a specific effect on the low serum calcium in these cases but the dose would have to be controlled carefully by serum calcium determinations Correction of the associated anemia administration of hydrochloric acid if this is lacking in the gastric secretions and supplying adequate amounts of calcium in the diet would be essential Parathyroid hormone produces only transient effects on the tetany in these cases

PHOSPHATE TETANY

Accumulation of inorganic phosphorus in the blood will force the blood calcium content down and Albright and his coworkers (1929) have indicated that this may be the primary factor in hypocalcemia of parathyroprivia Intravenous injections of phosphate will produce tetany In uremia phosphorus retention may be the cause of the tetany occasionally seen Tetany in non rachitic infants may be associated with a high content of inorganic phosphate in the blood

In this connection it should be mentioned that injection of sodium citrate may cause tetany by inactivating the serum calcium without changing its total calcium content and injection of sodium oxalate may cause tetany by actually precipitating and reducing the total amount of serum calcium This mechanism scarcely would be expected to be encountered clinically

Holtz fraction of irradiated ergosterol known as dihydrotachysterol or 'A T 10' might be useful in an occasional resistant case but very careful control of the dose by frequent serum calcium determinations would be essential because of its marked toxic effects if hypercalcemia is produced This substance does not possess the antirachitic property of the total irradiated ergosterol preparations and the rickets would require supplementary treatment In view of the excellent results obtained with natural vitamin D as found in standard preparations of cod liver oil it would be wise to adhere to the use of a good cod liver oil in the treatment of the vast majority of cases of infantile tetany

It has been found that acid producing substances such as ammonium chloride 4 to 6 grams (gr 60 to 90) by mouth daily and hydrochloric acid 75 c c (℥2½) of tenth normal acid daily in milk are effective in causing symptoms of tetany to disappear These however scarcely can replace the more effective calcium salts in the treatment of infantile tetany

Idiopathic Tetany

From 1880 to 1895 certain European cities particularly Vienna Heidelberg and Paris exhibited an unusual number of cases of tetany affecting particularly such indoor workers as shoemakers and tailors The disorder was most prevalent during the late winter particularly in March and April and disappeared during the summer months Leicher in an isolated instance of idiopathic tetany affecting an upholsterer in March 1922 demonstrated a reduction of blood calcium content and relief of symptoms when calcium salts were administered The prevalence of the disorder at the end of the winter season and particularly among indoor workers suggests that vitamin D deficiency must have been an important factor in the etiology Dietary deficiency in calcium may well have been present among this class of people at that time

Tetany of Pregnancy and Lactation

The demand during pregnancy for calcium for the fetal skeleton and during lactation for calcium in the milk secreted produces a potential calcium deficiency which when coupled with insufficient calcium intake and insufficient vitamin D may produce hypocalcemia and tetany It is rather remarkable that the disorder is not seen more frequently among the childbearing women The obvious remedy is the giving of calcium salts in large and long continued doses and the administration of vitamin D

feel puckered and thick making articulation difficult and the eyes may be narrowed assuming the expression of squinting The entire face feels tight and drawn Compression of the arm above the elbow greatly increases the tingling sensation in the hand and if maintained for from one to three minutes will result in a spasm of the hand with the fingers straight and stiff but partially flexed at the metacarpal phalangeal joints the thumb adducted into the palm and the wrist flexed The intensity of the spasm varies in different individuals If the overventilation is great enough and is continued for ten to twenty minutes spontaneous spasm of the hands will appear At first this can be overcome voluntarily but as it increase the hands become fixed in the typical position of carpal spasm Some subjects develop a similar but less marked spasm of the feet A very tight sensation in the upper part of the chest is not uncommon After prolonged hyperpnea forty five to sixty minutes laryngospasm has been observed and in one instance a complete tetanic convulsion lasting only about thirty seconds At any time after the first few minutes of deep breathing the electrical irritability is found to be increased All the active symptoms disappear very rapidly when the overventilation is stopped but the paresthesia may persist for five or ten minutes and the Chvostek sign still may be positive fifteen to thirty minutes later During the hyperpnea there is quite a marked diuresis

Tetany Following Overdosage with Sodium Bicarbonate

Overdosage with sodium bicarbonate upsets the $\frac{NaHCO_3}{H_2CO_3}$ *ratio to the* alkaline side just as does over breathing but it does so by increasing the numerator whereas in hyperpnea the denominator is decreased

Sodium bicarbonate and other alkalies are given to patients for a great variety of disorders and yet it is extremely rarely that clinical alkalosis and symptoms of tetany appear This is due to the fact that in individuals with normal renal function the mechanism of maintaining acid base equilibrium is very efficient and the excess of alkalie is excreted rapidly and otherwise compensated for Enormous doses of alkalie must be given before tetany will appear but nevertheless this occasionally happens particularly during the treatment of peptic ulcer with increasing doses of alkalie to neutralize free hydrochloric acid in the gastric juice Symptoms rapidly disappear when the administration of alkalie is stopped Healy (1921) has reported seven cases of tetany in post operative patients who were given through an error 160 grams of sodium bicarbonate by

ALKALOSIS TETANY

Tetany of Hyperpnea

Overbreathing to the extent that tetany is produced may be done voluntarily may occur as a result of purely functional disorders or occur in some rare instances in association with a disturbance in the respiratory center of the brain as has been observed in lethargic encephalitis It has been shown that hyperpnea removes carbonic acid from the body to an extent that the $\frac{NaHCO_3}{H\,CO_3}$ ratio in the blood is unbalanced and the blood actually becomes more alkaline

Tetany of hyperpnea is rather frequent in occurrence clinically but it often is not recognized Nervous and emotional individuals may over breathe during states of fear anger or anxiety and particularly during or in anticipation of pain When once started the carpopedal spasms and the paresthesias in the face and extremities increase the hysterical individual s fears and the overbreathing becomes more marked thus increasing the alkalosis and the tetany This vicious circle continues until the patient stops overventilating either as a result of reassurance or upon cessation of the exciting factors or perhaps as a result of pure exhaustion Usually the physician can end the attack immediately by a reassuring manner and by asking the patient to hold his breath for a short time after each inspiration Carbon dioxide will reaccumulate rapidly in the blood and the symptoms will disappear quickly As this occurs the physician must insist that the patient breathe quietly If the patient will not or cannot co-operate he may be made to rebreathe the expired air by improvising a funnel of paper to be held over the patient s face until the symptoms subside

Overbreathing may occur during the stage of excitement in anesthesia or during an attack of epilepsy to an extent that tetany develops Voluntary forced breathing in normal individuals produces all of the symptoms of tetany The subject should breathe as deeply as possible but the rate need not be more than fourteen to twenty per minute Within two or three minutes he will notice a tingling and prickling sensation either in the hands or face often in both and sometimes in the feet This paresthesia rapidly increases At about the same time it is possible to elicit a Chvostek sign of tetany In many subjects shortly there will be spontaneous contractions of the facial muscles the circular muscles about the mouth and eyes are involved chiefly and as a result the lip

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uremia All of these cases developed severe tetany the first four expired in convulsions the last three were treated with calcium lactate by mouth and recovered

In patients with markedly reduced renal function it may be less difficult to induce an alkalosis When the function is so reduced that the kidneys are unable to excrete the normal excess of acid products of metabolism and an acidosis develops the clinician may administer alkalies Occasionally it will be found that a relatively small excess of alkalie will change the acidosis to an alkalosis the kidneys being as inefficient in getting rid of the excess of alkalie as they were in excreting the normal excess of acids The spasms in this type of tetany may be very severe Instances have been reported in bichloride of mercury poisoning toxemia of pregnancy with greatly reduced renal function and in the toxic nephritis of severe burns Apparently it is more common in the acute nephritides It would seem logical to treat the tetany in these cases by a cautious administration of some acid producing substance such as ammonium chloride or hydrochloric acid itself

Gastric Tetany

Patients suffering with frequent and prolonged vomiting as a result of pyloric or upper intestinal obstruction frequently will exhibit tetany as a complication The mechanism is loss of hydrochloric acid with consequent lowering of the blood chloride elevation of the carbon dioxide capacity and increase in the alkalinity of the blood

Gastric tetany may occur as a result of obstruction in peptic ulcer or abdominal neoplasm and it has been observed in the persistent vomiting which occasionally follows a gastroenterostomy and in diaphragmatic hernia with vomiting In some instances there has been reported simply dilation of the stomach for which no mechanical cause was found

At the time these symptoms appear the patient often is already in a precarious condition from the underlying disease and the tetany may be only slight and incidental or it may be very severe and distressing The patient will be found some morning with the typical carpal spasm of tetany which may be painful and sometimes prevent voluntary motion of the hands The attack may be transient and recur at short intervals or there may be severe attacks of cramps involving the entire arm and sometimes the feet and legs as well lasting for hours or days with exacerbations Patients with chronic partial obstruction have had attacks at irregular intervals for a number of years

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CHAPTER XL

THE CLINICAL EXAMINATION OF THE CEREBROSPINAL FLUID

By CHARLES BRENNER AND H HOUSTON MERRITT

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Circulation — The fluid formed in the ventricles passes out through the foramina of Luschka and possibly the foramen of Magendie into that part of the subarachnoid space known as the cisterna magna Thence it passes into the other basal cisterns down over the cord to the lumbar sac or up over the cerebellum under the tentorium and over the cerebral hemispheres It is eventually reabsorbed into the venous circulation through the arachnoidal villi in the large dural sinuses

Composition — The cerebrospinal fluid normally is clear and colorless with approximately the same viscosity and surface tension as water Its osmotic pressure and pH are identical with those of blood plasma Since it contains very little protein however its total solid content is much lower than that of plasma approximately 1 gm per 100 c c The specific gravity of the fluid varies from 1 00 to 1 009 being somewhat lower in the ventricles than in the lumbar sac

In Table I are listed the normal values given by Merritt and Fremont Smith[2] for the various constituents of the lumbar cerebrospinal fluid which are of clinical importance Certain comments about this table are in order In the first place the qualification lumbar is important For example the protein content of fluid removed from the cisterna magna is about half that of lumbar fluid while ventricular fluid normally contains only very small amounts of protein up to 5 mgm per 100 c c In the second place the glucose and chloride contents of the cerebrospinal fluid are directly related to the concentration of glucose and chloride in the blood plasma with which the fluid is in equilibrium A patient with a high (diabetes glucose infusion) or a low (insulin shock hyperinsulinism) blood sugar will have a correspondingly high or low cerebrospinal fluid sugar and variations in the chloride content of the plasma (vomiting uremia Addison s disease debilitating infections) will be reflected similarly in the chloride content of the cerebrospinal fluid

Normally no erythrocytes are to be found in the cerebrospinal fluid The precise number of leucocytes which may be normally present is not certainly known A commonly used empirical rule is that a lumbar fluid containing five or more leucocytes per cubic millimeter is to be considered abnormal

Pressure — In the lateral recumbent position the pressure of the cerebrospinal fluid is equal in the lumbar sac the cistern and the ventricles Normal pressures in this position range in adults from 70 to 160 mm of water Pressures above 200 mm are definitely abnormal while pressures between 160 and 200 mm are suggestively high

Any change from the horizontal markedly influences the cerebro

Anatomy and Physiology of Cerebrospinal Fluid

General Consideration — The cerebrospinal fluid is found in the cerebral ventricles and in the subarachnoid space of the meninges It is thus in intimate contact with the inner and outer surfaces of the neuraxis and also has at least potential access to the substances of the central nervous system by way of the perivascular spaces The normal amount of the fluid varies with age and from person to person In adults there are usually from 90 to 150 c c The function of the fluid is assumed to be essentially mechanical, to help support the weight of the neuraxis to damp any oscillations of the brain within the skull and to protect it against the force of blows from without

Formation — The chief sources of origin of the cerebrospinal fluid are the choroid plexuses Some authors assume that contributions to the fluid are made also from the perivascular spaces and from the ependymal cells of the brain and spinal cord but these assumptions as yet lack any convincing proof[1]

For many years there was great controversy over the mechanism of formation of the cerebrospinal fluid that is whether it was an ultra filtrate or dialysate similar to the glomerular filtrate of the kidneys or whether it was a secretion of the cells of the choroid plexuses Although this question still is not settled beyond possibility of doubt the great weight of evidence seems to be on the side of dialysis or ultra filtration, since it offers the simplest adequate explanation for most of the known facts about the composition of the fluid and there are no facts which necessarily contradict it

Examination of Cerebrospinal Fluid

The examination of the cerebrospinal fluid is the most valuable single laboratory aid in the field of neurological disorders. When properly performed, it is a simple, safe and painless procedure, and every physician who may be called upon to diagnose diseases of the nervous system should know the following points about the technique of examination of the cerebrospinal fluid and should be able also to interpret the results of the examination properly.

Method of Obtaining Fluid.—In clinical practice lumbar puncture is the method of choice for obtaining cerebrospinal fluid and studying its pressure and dynamics. Cisternal puncture, because of the greater risk involved, is best left to the expert, while ventricular puncture is a surgical procedure, although in infants with open fontanelles it may be done by the expert as a bedside procedure.

There are few contraindications to performing a lumbar puncture. As in the use of any special diagnostic procedure, the investigator should have a clear idea of what help he may hope for from the puncture. The paragraphs which follow on the interpretation of the results of the examination of the fluid outline what information can be obtained from such an examination. If none of this information is helpful or necessary in the diagnosis of a particular case, spinal puncture obviously is superfluous. Such elementary considerations should govern also the performance of the various parts of the examination of the fluid. For example, if a patient being treated for syphilis is to have a routine examination of his cerebrospinal fluid, there is no useful purpose served by measuring the pressure of his fluid. Since it is necessary to use a relatively large bore needle to measure the pressure, and since the use of a large needle is much more likely to be followed by headache than is a smaller one, it is obviously not good clinical judgment to subject this particular patient to the needless procedure of measuring the pressure of his fluid.

In patients with signs and symptoms of an *intracranial neoplasm*, if there is a high degree of papilledema, lumbar puncture often should be omitted, particularly if the results of puncture are unlikely to influence the diagnosis, as is usually true in such cases. If a puncture is performed, care should be taken that fluid is removed slowly, one drop a second, and that the final pressure is not less than *one half the initial pressure*.

If the skin or subcutaneous tissue of the back is grossly infected, it is obvious that a needle should not be passed through the infection into

spinal fluid pressure. For example, in the erect position the pressure in the cisterna magna is zero, i.e. equal to atmospheric pressure, that in the ventricles is slightly lower, while the lumbar pressure rises to 300 to 400 mm, depending on the distance from the base of the skull to the site of puncture[3]. For this reason the pressure of the cerebrospinal fluid always should be determined in the lateral recumbent position and so recorded unless otherwise specified.

TABLE 1

NORMAL VALUES IN THE LUMBAR CEREBROSPINAL FLUID OF CHEMICAL CONSTITUENTS WHICH ARE OF CLINICAL IMPORTANCE

Constituent	*Normal Value in Milligrams per 100 Cubic Centimeters*	
Glucose	[illegible]	(50 to 80 per cent of blood sugar value)
Chloride	697 — 748	(expressed as NaCl about 1.0 per cent of serum chloride content)
Total Proteins	15 — 45	

Cerebrospinal fluid pressure is directly related also to venous pressure. If the venous pressure is raised for any reason the large intracranial veins and the venous plexuses of the spinal canal become distended and the pressure within the inelastic dural sac promptly rises to the same level as the venous pressure. Similarly, if these venous structures are collapsed by a rapid lowering of the venous pressure, for example by a brief period of forced respiration which temporarily lowers the venous pressure, the cerebrospinal fluid pressure also will drop promptly. Arterial pressure, however, does not affect cerebrospinal fluid pressure, presumably because the larger intracranial and intraspinal arteries are thick walled inextensible structures.

Any factor which affects the filtration pressure in the capillaries of the choroid plexuses will change the rate of formation of the cerebrospinal fluid and thus will alter gradually the cerebrospinal fluid pressure, at least until equilibrium is re-established between the rates of formation and absorption of the fluid. The best understood of these factors is the osmotic pressure of the plasma. If this falls, i.e. if the plasma becomes more dilute, cerebrospinal fluid will be formed more rapidly than before and its pressure will rise. Vice versa, if the plasma osmotic pressure rises the cerebrospinal fluid pressure will fall.

EXAMINATION OF CEREBROSPINAL FLUID

The examination of the cerebrospinal fluid is the most valuable single laboratory aid in the field of neurological disorders When properly performed it is a simple safe and painless procedure and every physician who may be called upon to diagnose diseases of the nervous system should know the following points about the technique of examination of the cerebrospinal fluid and should be able also to interpret the results of the examination properly

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If the skin or subcutaneous tissue of the back is grossly infected it is obvious that a needle should not be passed through the infection into

the subarachnoid space, as such a procedure would be very likely to produce a meningitis

Technique — The technique of lumbar puncture is as follows The patient is instructed to lie on his side close to the edge of the bed and to flex maximally his hips and knees on the one hand and his neck and shoulders on the other When he has thus 'rolled himself up into a ball', the operator or his assistant moves the patient so that the lower part of his back is at the very edge of the bed and parallel to it Having the patient in this position greatly facilitates the task of determining the precise angle to the back at which the needle is to be introduced The desired lumbar interspace is then located by palpation with reference to the iliac crest which normally is opposite the spine of the third lumbar vertebra and the spot at which the needle is to be introduced may be conveniently marked by the thumbnail The site of puncture and the surrounding skin then is cleansed with a suitable antiseptic e g a 2 per cent alcoholic solution of iodine, and with alcohol and the operator's hands either scrubbed surgically or encased in sterile gloves A drop of 2 per cent novocaine then is injected intracutaneously with a very fine gauge needle precisely at the proposed site of the puncture After anesthesia of the skin has been established the subcutaneous and deeper *interspinous tissues are infiltrated also with* 2 per cent *novocaine Five* cubic centimeters usually are ample for this purpose

If the pressure and dynamics are to be measured the most convenient type of needle to use is one in which the three-way stopcock is soldered into the butt of the needle and the stylet is made long enough to pass through both stopcock and needle The needle itself should be at least 20 gauge, preferably 19 to permit ready passage of fluid between the subarachnoid space and the manometer which measures the pressure The simplest satisfactory type of manometer is composed of two (for very high pressures three) sections of narrow bore graduated glass tubing each with a male fitting at the lower end and a female one at the upper to permit assembly and attachment to the three way stopcock

The sterilized needle with stylet in place is inserted in a plane perpendicular to the back and is directed slightly cephalad to allow for the angulation of the spine produced by the normal lumbar curve Resistance is felt as the needle passes through the ligamentum flavum and again as it encounters the dura The slight "give" as the needle passes through the dura usually is perceptible easily after some practice When the dura *has been penetrated the stylet is withdrawn the stopcock turned* so as to prevent escape of fluid and the manometer tubes attached if the

pressure is to be determined If no fluid appears at the butt of the needle when the stylet is withdrawn even when the patient coughs or strains to raise the pressure of the fluid the needle may be rotated slightly or withdrawn or advanced a short distance Rotation and withdrawal may be performed with the stylet out but the stylet should be in the needle whenever it is advanced

Pressure —Measurement of the pressure is carried out as follows When the needle is in place the patient is permitted to relax his legs and neck to whatever position is comfortable and his head is supported on a low pillow He remains of course in the lateral recumbent position He is reassured and asked to relax the manometer tubes are adjusted and the stopcock is turned to permit the fluid to pass into the manometer The first important technical error to be considered is the absence of free communication between the subarachnoid space and the manometer To insure against this the patient s abdomen is compressed or he is asked to strain Either of these maneuvers should be accompanied by a rapid rise of the fluid level which will fall as the abdominal pressure falls This is the only purpose and significance of abdominal compression in lumbar puncture to prove the existence of free communication between the manometer and the subarachnoid space In the case of cisternal puncture jugular compression serves the same purpose

The second important technical problem is to ensure adequate relaxation on the part of the patient If he is not properly relaxed he is in the position of straining more or less and as a result the intra abdominal venous pressure is elevated and with it the cerebrospinal fluid pressure The legs should be straightened to relieve the compression on the abdomen Instructing the patient to breathe through his mouth as is commonly done may be helpful in getting him to relax but it must be remembered that a succession of deep breaths will artificially lower the systemic venous pressure and as a result the cerebrospinal fluid pressure will drop temporarily below its true value In the last analysis if there is any question whether the patient is properly relaxed the only way to be certain is to wait patiently by his side for twenty minutes talking to him the while With rare exceptions this procedure will insure adequate relaxation

Dynamics —In order to test whether or not there is free communication between the fluid in the lumbar sac and that in the cisterna magna presence or absence of spinal block the jugular veins are compressed in the neck either digitally or by means of a sphygmomanometer cuff which has been wrapped about the neck and inflated to a pressure of 40

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Laboratory glassware varies considerably in color and this point is of practical importance

The presence of blood in the cerebrospinal fluid may cause the sample to appear opalescent pink or bloody depending on the amount of blood present As noted above if the blood has resulted from the puncture usually it is not evenly mixed with the fluid Moreover if such fluid is centrifuged the supernatant fluid will be colorless or nearly so the plasma proteins may of course impart some color to the fluid If the blood has been mixed already with the fluid for a few hours or longer however the erythrocytes will have begun to disintegrate and the supernatant fluid in a centrifuged specimen will be definitely xantho chromic

Turbidity of the fluid indicates the presence of large numbers of cells or bacteria which *of course* should be counted and identified micro scopically The significance of leucocytosis is discussed below In rare instances turbidity may be caused by the presence of very large numbers of bacteria in the fluid

Cellular Content — The number of cells in the cerebrospinal fluid usually is counted by placing the undiluted fluid in a conventional hemocytometer chamber and counting all the cells in the nine largest squares This figure then is multiplied by the factor 10/9 If the number of cells is very great it becomes necessary to dilute the fluid in a blood pipette and proceed as with an erythrocyte or leucocyte count in the blood

It takes but little practice to distinguish between erythrocytes and leucocytes in the counting chamber Much more practice is required however to differentiate among the different types of leucocytes In order to facilitate such differentiation a drop of polychrome methylene blue Unna s stain often is added to the fluid before it is placed in the counting chamber but even this help is not sufficient to insure accuracy In fact the only satisfactory way to differentiate certainly among the various types of leucocytes is to centrifuge a specimen of the fluid smear the sediment on a slide and stain it with Wright s or some similar stain

Qualitative Tests for Protein — Two final tests which are designed to indicate the presence in the fluid of increased amounts of protein often are performed by the operator The first of these is the Pandy test in which the reagent is a saturated solution of phenol in water A drop of reagent and a drop of cerebrospinal fluid are placed side by side on a watch glass and are allowed to run together The appearance of more

to 80 mm of mercury. If jugular compression produces a prompt rise in lumbar pressure and jugular release a prompt fall, it is clear that no dynamic block exists. If on the other hand there is no rise on jugular compression or only a slow and incomplete one, then one can postulate a lesion somewhere between the neck and the lumbar sac, which either wholly or partly blocks the passage of the cerebrospinal fluid. It is of course essential to be sure that the response to abdominal compression is prompt and adequate, that is that the manometer is recording correctly the pressure within the lumbar sac. If the initial pressure is unusually low (below 80 mm of water), abnormalities in dynamic tests are of little significance. If a cisternal puncture is done, of course, it is jugular compression which proves the accuracy of the readings and the response to abdominal compression which indicates the presence or absence of dynamic block. Finally, when a lumbar puncture is done in a patient in whom there is no question of a spinal cord lesion, e g a brain tumor suspect, it is needless and in some cases perhaps even dangerous to subject the patient to jugular compression.

Collection of Sample — After the pressure and dynamics have been tested a sample of fluid should be removed for further examination. If the initial pressure is high the fluid should be removed slowly, one drop a second, and if the cause of the high pressure is suspected to be an intracranial mass the final pressure should be at least half the initial pressure. Otherwise the fluid can be allowed to run off freely until a suitable sample for routine purposes 8 to 15 c c has been collected. The fluid may be collected conveniently in three clean, preferably sterile tubes. In the first tube is collected about 1 c c for the cell count and rough protein determinations, in the second [illegible] to 6 c c for the more accurate chemical analyses, total protein and if indicated sugar and chloride, and in the third 6 to 8 c c for one of the serological tests for syphilis and for a colloidal test, gold solution, gum mastic, etc. The three tubes method of collection often is helpful in deciding whether a bloody fluid is the result of the puncture itself, "bloody tap", or whether it was caused by a spontaneous hemorrhage or by trauma before the tap. In the former case the fluid in the first tube usually is bloodier than that in the third, while in the latter case the fluid is equally bloody in all three tubes.

Color and Clarity — The first examination of the fluid after removal is that of inspection. Even slight degrees of xanthochromia are of importance to note, and for this purpose one must be careful to compare the fluid with a sample of clean water in another test tube of the same color

tion with any widespread inflammation of the meninges or ependyma presumably because of the addition of considerable amounts of inflammatory exudate to the cerebrospinal fluid

The amount of cerebrospinal fluid may be increased also by any process which interferes with its absorption into the venous system through the arachnoidal villi of the dural sinuses Such processes usually are chronic or congenital and the persistent increase in the amount of fluid which results from them usually is called hydrocephalus Hydrocephalus may be of two types communicating and noncommunicating In the communicating type there is a free flow of fluid through all of the channels within the brain and between the fourth ventricle and the subarachnoid space in the basal cisterns but the exit of the fluid from these cisterns is prevented by the presence of meningeal adhesions In the noncommunicating type the fluid is confined within the ventricular cavities of the brain and is unable to reach the villi through which it should pass into the venous circulation Such a blocking of the normal circulation of the fluid may result for example from a tumor or exudate which occludes the foramen of Munro producing a unilateral hydrocephalus or the third ventricle Sylvian aqueduct fourth ventricle or foramen of Luschka producing a bilateral hydrocephalus

The volume of the solid contents of the dural sac may be increased also in a variety of ways by tumor or edema of the neuraxis or by formation of an abscess or hematoma It may be mentioned that a tumor or abscess of the brain may affect the intracranial pressure not only by its bulk but also by blocking the circulation of the cerebrospinal fluid If the volume of the dural sac is diminished by formation of an extradural mass e g a hematoma the cerebrospinal fluid pressure will rise also

It is important to remember that none of the conditions and diseases which we have mentioned with the single exception of elevated venous pressure can be excluded from the differential diagnosis if the cerebrospinal fluid pressure is normal A normal fluid pressure may be found in cases of brain abscess tumor intracranial hematoma or meningitis An elevated pressure may be good evidence in favor of one of these diagnoses but a normal pressure does not exclude any of them

Dynamics—The significance of an abnormal response to the dynamic tests on the cerebrospinal fluid is simple once the examiner has assured himself that the abnormalities are genuine They indicate the presence of some process occluding or compressing the dural sac between the cisterna magna and the point of puncture in such a way as to block the movement of spinal fluid either partially or completely Such a

than a very faint turbidity indicates that the protein content of the fluid is abnormally high The second is the ammonium sulfate test which is performed by layering a saturated solution of ammonium sulfate under a sample of cerebrospinal fluid in a small test tube The test is read in one to two minutes The appearance of turbidity at the juncture between fluid and reagent indicates that the globulin content of the fluid is abnormally high It should be emphasized that these are rough tests, whose only value is simplicity and speed A quantitative determination of the protein content of the fluid is essential for accurate diagnosis and when available it supersedes completely either of the other two tests

Other Tests — The quantitative chemical determinations and the serological and colloidal tests must be performed by a trained technician in a suitably equipped laboratory and any description of their technique is beyond the scope of this presentation For such a description the reader is referred to the text of Merritt and Fremont-Smith

Interpretation of Results of Examination of Cerebrospinal Fluid

We shall now discuss briefly the significance of the results of the various examinations described above

Pressure — An abnormally elevated initial pressure may be due to an increase in venous pressure If this possibility can be ruled out an elevated initial pressure indicates either an increase in the fluid or solid contents of the dural sac or impingement on the sac from without

Let us consider first the ways in which the amount of cerebrospinal fluid can be increased Perhaps the simplest possibility is the sudden addition of an extra amount of fluid to the ventricular or subarachnoid space This addition may be on a mechanical, chemical or inflammatory basis If a sizable blood vessel for example is torn or ruptured and the blood mixes with the cerebrospinal fluid, it is obvious that the fluid pressure must rise This of course, is a simple mechanical process On the other hand if the blood plasma is chemically altered in such a way that its osmotic pressure is suddenly lowered the rate of formation of cerebrospinal fluid will be increased correspondingly and a considerable increase may result in high fluid pressure Such a process often occurs in children at the onset of any acute infectious disease when the plasma chlorides drop sharply and a condition known clinically as meningism results Finally it is usual to have an increased fluid pressure in connec

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sugar level is normal a cerebrospinal fluid sugar level of less than 40 mgm per 100 c c is with few exceptions indicative of meningitis of bacterial origin Syphilitic meningitis is not accompanied by a decrease in the glucose content of the fluid and this constitutes an important differential diagnostic point Various bacteria uniformly metabolize the glucose in the fluid as do the yeasts which rarely are the cause of meningitis Viruses on the other hand do not metabolize glucose and in virus meningitides the fluid sugar content is normal or even slightly elevated It goes without saying that a sterile inflammation of the meninges or ependyma is associated with a normal glucose level in the fluid One word of warning must be uttered about the interpretation of the glucose level Nowadays nearly all patients with fever are started promptly on penicillin or one of the sulfonamides or both In a case of bacterial meningitis if the infecting organism is sensitive to antibiotic or the drug used the infection may have been sufficiently checked by the time the puncture is done for the glucose content to be normal despite the persistance of an increase in pressure an increased cell count and elevation of the protein content

Chlorides — Other chemical tests on the fluid are of minor importance The chloride content has in the past been considered to be of considerable significance and the statement may still be found occasionally in the literature that a very low chloride content is diagnostic of tuberculous meningitis Unfortunately this idea is quite false It is true that patients with tuberculous meningitis do regularly have low chloride levels in the cerebrospinal fluid but so does any other patient with a chronic severe meningitis In fact a low chloride level is only indicative of a serious long continued infection

Tests for Syphilis — Serological tests for syphilis on the cerebrospinal fluid are of the conventional type and are performed usually on several different dilutions of the fluid The smaller the amount of fluid necessary to give a positive reaction the more intense the syphilitic process is presumed to be With few exceptions a positive reaction in less than 1 c c of fluid is indicative of central nervous system syphilis The most frequent source of error is caused by the leakage of plasma protein containing syphilitic reagin into the cerebrospinal fluid Thus if a patient with a positive blood serology has a cerebrospinal fluid protein level above 75 mgm per 100 c c for any reason e g tumor meningitis or hemorrhage the fact that his cerebrospinal fluid serology is also weakly positive should not be considered to be absolute proof of central nervous system syphilis[4]

process may be tumor, edema or inflammation of the cord adhesions of the meninges, extramedullary tumor or granuloma or compression by a spinal fracture

Color and Clarity —Xanthochromia usually is indicative of the presence of changed hemoglobin, i e of previous bleeding into the subarachnoid space A very high protein content will impart also a yellow color to the fluid In jaundiced patients the fluid sometimes also is colored yellow The nature of the pigment responsible for this is not known

A pink or red color in the fluid of course, indicates recent bleeding into the ventricular or subarachnoid space The source of the bleeding may be a parenchymal vessel or one in the meninges

Cellular Content —The presence of erythrocytes on microscopic examination is of course also indicative of bleeding into the cerebro spinal fluid A leucocytosis on the other hand indicates the presence of inflammation in or close to the ependyma or meninges The more acute and widespread the inflammation and the closer it is to the fluid spaces the higher the cell count is likely to be and the higher the pro portion of polymorphonuclear cells It is important to emphasize that inflammation is not synonymous with infection Sterile inflammation for example can occur about a tumor or an area of infarction and thus produce a leucocytosis Similarly foreign bodies of many sorts elicit an inflammatory reaction and one of the most common of these is blood in the ventricles or subarachnoid space The leucocytosis produced by such blood lasts for four or five days after the disappearance of the erythrocytes, so that for example in the case of a traumatic puncture bloody tap" one cannot attach diagnostic significance to a slight pleocytosis until after five days have passed

Protein —An increase in the protein content of the fluid occurs in association with the pleocytosis in inflammatory conditions The protein content of the fluid may be elevated in the absence of pleocytosis or out of proportion to it in cases of brain tumor in certain types of polyneuritis of unknown etiology and in some infections, e g in the late stage of acute anterior poliomyelitis In addition stasis of fluid as a result of a spinal block will produce an increase in the protein content of the stagnant fluid which may reach 2 to 4 mgm per 100 c c In such cases the stagnant cerebrospinal fluid gradually approaches the composition of blood serum

Sugar —The glucose content of the cerebrospinal fluid is of value because of the information it affords in cases of meningitis If the blood

the tabetic curve but this term has been discarded This type of curve may be found in any abnormal fluid and is not diagnostic of any disease

End zone Curve — The third type of reaction is one in which the most color change occurs in the tubes with the least concentration of cerebrospinal fluid This is called the end zone curve Examples are 0011233333 or 0001223444 This type of curve is most common in fluids with a very high protein content

Bacteriological Studies — Bacteriological studies of the cerebrospinal fluid are of the same types as those performed on any other body fluid and the results of the studies have the same significance The same is true for the various immunological studies other than those for syphilis For this reason no special discussion of these studies seems in order at this point

Special Diagnostic Tests — The cerebrospinal fluid spaces in and about the neuraxis may be outlined roentgenographically by replacing the fluid with a suitable contrast medium The medium usually used to outline the intracranial spaces is air and the procedure is called pneumoencephalography (Figs 1 and 2) To outline the spinal subarachnoid space myelography (Fig 3) either air or a relatively radio opaque substance such as lipiodol may be used

In *pneumoencephalography* (Figs 1 and 2) a needle is inserted either into the lumbar sac or into the cisterna magna while the patient is maintained in a sitting position and all or part of the cerebrospinal fluid is replaced by air This may be done through a single needle from which the fluid is allowed to drain in 10 to 20 c c lots and through which air is injected by means of a syringe in equal amounts An alternative procedure with certain technical advantages is to perform two lumbar punctures on the patient one above the other With the two needles in place an attempt is made to maintain a constant pressure during replacement by introducing air through the upper needle while fluid is allowed to escape from the lower one Several types of apparatus have been described by means of which the fluid may be replaced automatically with air The principle of any such apparatus is quite simple Cerebrospinal fluid drains from the lower needle through a tubing into one of two openings in an otherwise closed bottle This fluid displaces an equivalent volume of air from the bottle through the other opening and thence through the upper needle into the subarachnoid space

Roentgenograms may be taken with the patient in the erect or recumbent position Routine stereoscopic antero-posterior and right and left lateral exposures should be made as soon after the introduction

Colloidal Tests — Of the various colloidal tests on the cerebrospinal fluid the gold sol test devised by Lange is the most widely used All of the colloidal tests, when positive, probably indicate the presence in the fluid of an abnormal type or amount of globulin The majority of abnormal reactions are caused simply by a high protein content of the fluid but they may occur in fluids with a normal total protein In such cases there is likely to be a disturbance of the albumin globulin ratio and/or the type of globulin present The most notable of the diseases of the central nervous system in which this may occur, are syphilis and multiple sclerosis However the abnormality in the cerebrospinal fluid globulin may be merely a reflection of a similar abnormality in the metabolism of the plasma proteins as for example in myxedema or nephritis and such systemic diseases may be accompanied also by positive colloidal reactions in the cerebrospinal fluid However, the chief source of difficulty in interpreting the colloidal tests is the unreliability of their results except when done by a technician who is specially skilled in performing them If the tests are performed by anyone less than an expert the clinician is safest, if he disregards them entirely in reaching his diagnosis

With these reservations we may proceed to a brief discussion of the diagnostic significance of the different types of gold sol reactions The reactions in the other colloidal tests are roughly similar and will not be detailed

First-zone Curve — The reactions that are found in the cerebrospinal fluid commonly take one of three forms In the first the greatest change is in the tubes with the highest concentration of the cerebrospinal fluid Complete precipitation and decolorization is most likely to occur in this type of reaction with readings (curves) as follows 5555443211 55433-1100 or 44332-1000 This type of curve is spoken of as the first zone or paretic' curve, it is best to avoid the use of the term paretic' curve because of its prejudicial significance While this type of curve is found almost constantly in patients with dementia paralytica it is quite common also in other types of syphilis of the nervous system and in nonsyphilitic disease such as multiple sclerosis and acute encephalomyelitis Also it is seen occasionally in patients with brain abscess brain tumor polyneuritis cerebral hemorrhage etc

Mid-zone Curve — The second type of curve is characterized by the most marked change occurring in the third to sixth tubes Complete decolorization is rare and examples of such curves are 1-4433 100 or 1-33321000 This is called the mid zone" curve It was formerly called

of the air as possible since it begins to be absorbed into the blood stream as soon as it is introduced In cases of suspected temporal lobe lesions lateral stereoscopic views are taken with the patient recumbent and the suspected lobe uppermost If the occipital horns are the object of special interest exposures are made with the patient lying face down on the cassette *Exact centering of the patient s head for all pictures is essential* The entire procedure may be wasted by failure to obtain true lateral and exact antero-posterior roentgenograms

The usual aim in performing pneumoencephalography is to replace the fluid by air as completely as possible so as to ensure complete filling of the ventricles and subarachnoid spaces Much of the information given by such a complete pneumoencephalogram may be gained by introducing a bubble of 20 to 30 c c of air intracisternally after re *moving an equal amount of fluid This procedure has the advantage* that it is much less disturbing to the patient than the classic one and the disadvantages that it usually shows only the ventricles and may not even do that When it is successful the bubble of air outlines only the upper most portion of the ventricles so that a number of views is necessary to outline the whole system Familiarity with the pictures of complete filling is necessary for interpretation

Pneumoencephalography besides causing the patient considerable *headache is not without dangers and should not be embarked upon* without diagnostic objective Its value in the treatment of post trau matic headache is doubtful[3]

Pneumomyelography is of value in demonstrating the lower level of complete subarachnoid block and in outlining the lumbar and caudal *subarachnoid space In performing it gas should be evacuated from the* intestines as for scout films of the abdomen Lumbar puncture is per formed with the patient on an x ray tilt table From 40 to 50 c c of spinal fluid is removed and the table is tilted so that the pelvis is 15 degrees higher than the head Any fluid left in the lumbar sac is allowed to drain and a quantity *of gas air or oxygen equal to the total* amount of fluid removed is injected For this use a 50 c c syringe with rubber tube connection and introduce air slowly After the needle is removed the table is tilted until the pelvis is 25 degrees higher than the head and roentgen exposures are taken as indicated Fluoroscopy is not useful in this procedure The patient s *pelvis should be kept elevated above his* head for twenty four hours

Myelography by means of lipiodol pantopaque or other radio opaque oils is valuable (1) in locating the site of lesions of the spinal



Fig 1 Normal pneumoencephalogram

cord where complete or incomplete subarachnoid block has been demonstrated by lumbar or combined lumbar and cisternal punctures but in which exact localization and extent of the lesion causing the block cannot be determined by careful neurological examination and (2) in outlining lesions of the cauda equina (Fig 3) The use of lipodal or pantopaque should be restricted to those instances where localization by neurological means is impossible or where the results of air injection are unsatisfactory After completion of the test, the oil should be removed

Therapeutic Use of Lumbar Puncture

The chief value of lumbar puncture is diagnostic Removal of fluid is of inestimable value in the relief of intracranial pressure in patients with morbid conditions such as meningism acute purulent meningitis cerebral trauma and subarachnoid hemorrhage where the increase in pressure is of a temporary nature Removal of fluid is of value in maintaining a normal pressure in patients who have had a craniotomy for the removal of an expanding intracranial lesion (tumor abscess hematoma) but is of no value in such cases prior to operation Lumbar puncture is of importance for the introduction of anesthetics in spinal anesthesia and the introduction of contrast media as described above There is considerable controversy as to the advisability of its use for the introduction of sera drugs and antibiotics in the treatment of infections of the nervous system It has been claimed that these substances when administered by other routes do not pass into the cerebrospinal fluid in sufficient concentrations to be of therapeutic value There is not however any data to indicate that the therapeutic results obtained by the intrathecal administration of these substances is superior to those obtained by their administration by more usual routes On the other hand there is ample clinical proof that intrathecal administration of these therapeutic agents may be followed by serious damage to the central nervous system

At the present time intrathecal therapy has been discarded almost entirely except in the treatment of the more refractory meningitides e g those caused by the tubercle bacillus or by pyogenic bacteria When more effective agents for the treatment of these diseases are available it is quite probable that intrathecal therapy will be discarded entirely If such therapy is deemed necessary in any case at present it should be undertaken only with full realization of the risks involved



Fig 2 Pneumoencephalogram in patient with a left frontoparietal subdural hematoma Right ventricle displaced to right no filling of ventricle or cortical subarachnoid spaces on left side

Cerebrospinal Fluid Syndromes

Leptomeningitides

Acute purulent meningitis due to any of the pyogenic bacteria produces the following cerebrospinal fluid abnormalities high initial pressure (200 mm or over) marked pleocytosis (200 to 0 000 white blood cells per cu mm with a high percentage of polymorphonuclears) elevation of total protein in proportion to the pleocytosis progressively decreased sugar content (45 0 mgm per cent) moderately diminished chloride content (700 – 550 mgm per cent) and various abnormalities in the gold curve usually of the mid zone or end zone type Smear or culture permits identification of the infecting organism

Tuberculous meningitis is characteristically subacute rather than acute and the cerebrospinal fluid abnormalities are correspondingly less severe than those just described Initial pressure is elevated (00 mm or more) there is moderate pleocytosis (0 500 white blood cells per cu mm 5 50 per cent polymorphonuclears) protein content is increased (50 500 mgm per cent sugar content is nearly always low (45 25 mgm) and falls progressively although rarely it is normal early in the course of the disease chlorides are low and also fall progressively occasionally to below 500 mgm per cent and the gold curve is abnormal in about 70 per cent of the cases Tubercle bacilli may be identified by careful examination of a stained smear of the centrifuged specimen or of the clot that generally forms in the fluid on standing overnight Culture of the organisms on special media and guinea pig inoculation will establish the diagnosis

Syphilitic meningitis is also a subacute meningitis with slight to marked pleocytosis and increase in protein but the sugar and chloride content are normal or only moderately decreased (rarely below 35 mgm per cent for sugar and 650 mgm per cent for chloride) the gold curve is abnormal (first or mid zone) in 95 per cent of cases and the Wassermann reaction is regularly positive

Choriomeningitis (benign lymphocytic meningitis) is characterized by the following cerebrospinal fluid abnormalities slight to moderate increase in pressure in the majority of cases (200 350 mm) slight to marked pleocytosis (0- 000 white blood cells per cu mm) with 70 100 per cent lymphocytes slight or no increase in protein content (rarely over 70 mgm per cent) slight or no decrease in sugar content (rarely below 650 mgm per cent) and occasional abnormality of any

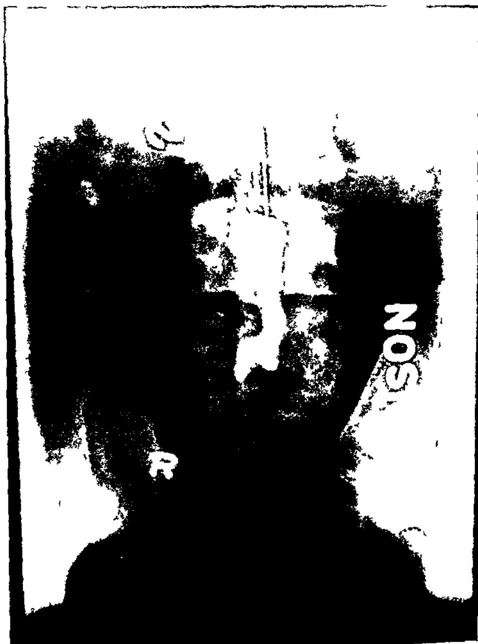


Fig 3 Myelography Defect in the pantopaque column at level of intervertebral disk between fourth and *fifth lumbar* vertebrae as result of rupture of nucleus pulposus

Cerebrospinal Fluid Syndromes

Leptomeningitides

Acute purulent meningitis due to any of the pyogenic bacteria produces the following cerebrospinal fluid abnormalities high initial pressure (200 mm or over) marked pleocytosis (00 to 20 000 white blood cells per cu mm with a high percentage of polymorphonuclears) elevation of total protein in proportion to the pleocytosis progressively decreased sugar content (45 0 mgm per cent) moderately diminished chloride content (700 – 550 mgm per cent) and various abnormalities in the gold curve usually of the mid zone or end zone type Smear or culture permits identification of the infecting organism

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type in the gold sol curve With suitable techniques the virus may be cultured from the cerebrospinal fluid or its presence inferred by sero logical test

Mumps meningitis, as evidenced by inflammatory changes in the cerebrospinal fluid, occurs in a very high percentage of patients with any form of mumps, including those with no clinical evidence of men ingeal involvement In both World Wars in the course of mumps epi demics in army camps observers have noticed cases which showed meningitis presumably due to a filtrable virus with no other signs of mumps i e no adenitis, orchitis or pancreatitis Such cases are presumed to be ones of pure mumps meningitis, although in the absence of ade quate serological or cultural tests for the disease, this presumption cannot be proved definitely The cerebrospinal fluid abnormalities in patients with mumps meningitis are identical with those just described for choriomeningitis except, of course, for the results of serological and cultural tests

Torula (yeast) meningitis is a rare disease which produces essentially the same cerebrospinal fluid abnormalities as tuberculous meningitis It is differentiated by the absence of tubercle bacilli and the finding of yeast organisms in stained smears or culture

Meningoencephalitides and/or Meningomyelitides

Syphilitic meningoencephalitis (dementia paralytica, general paresis) is the most severe of the syphilitic infections of the nervous system The cerebrospinal fluid abnormalities which are to be listed as characteristic of this form of neurosyphilis are those found in untreated cases With effective therapy any or all of the cerebrospinal fluid abnormalities may disappear These abnormalities are as follows, slight to moderate pleo cytosis (15-200 white blood cells per cu mm) chiefly lymphocytes moderate increase in protein content (50-150 mgm per cent) first-zone gold curve in 85 per cent of patients a mid-zone curve in the remaining 15 per cent and a strongly positive Wassermann reaction in a small amount of fluid (0 05 to 0 1 c c)

Tabes dorsalis also may be considered conveniently here although the exact nature of the pathological process i e the site of the syphilitic process responsible for the eventual destruction of the posterior columns of the spinal cord is as yet obscure The characteristic cerebrospinal fluid abnormalities in early active cases are not essentially different from

those accompanying syphilitic meningoencephalitis but since many patients are not examined until late in the disease when the acute inflammatory process has subsided the abnormalities in the fluid in the average are less severe These abnormalities are slight or moderate pleocytosis in 65 per cent (5 oo white blood cells per cu mm) chiefly lymphocytes slight or moderate increase in protein content in 50 per cent (50 150 mgm per cent) first zone gold curve in 10 per cent mid zone in 35 per cent and normal or doubtful in 55 per cent and a positive Wassermann reaction in 80 per cent but only in a large amount of fluid (0 0 6 c c) in many of these It is important to remember that tabes may be a self limited disease in which case after spontaneous cure has occurred the cerebrospinal fluid is entirely normal

Asymptomatic neurosyphilis is a clinical rather than a pathological diagnosis and is used to group together all patients with any cerebrospinal fluid abnormality attributable to syphilis of the central nervous system who nevertheless have no clinical evidence signs or symptoms of such involvement The cerebrospinal fluid abnormality may vary from nothing but a weakly positive Wassermann reaction to the complete picture of pleocytosis increased protein content first zone gold curve and strongly positive Wassermann reaction in a small amount of fluid

The cerebrospinal fluid abnormalities found in patients with syphilitic meningitis have been described already in the previous section

The logical consequence of the above paragraphs is this it is not possible to decide what type of neurosyphilis a patient has from the examination of the cerebrospinal fluid alone The most one can say as far as a single examination goes is that a weakly positive fluid makes the diagnosis of syphilitic meningoencephalitis very unlikely Much more can be inferred from the changes or lack of them in the cerebrospinal fluid over a period of time and in response to various forms of treatment but in most cases a satisfactory diagnosis can only be made by considering together all the available clinical historical and laboratory data

Septic emboli to the brain may complicate any pulmonary or cardiac infection Those coming from a pulmonary abscess or bronchiectasis frequently will give rise to a large cerebral abscess or an acute meningitis Those coming from subacute bacterial endocarditis usually will set up many small abscesses in the substance and on the surface of the brain which never grow very large but give rise to a rather characteristic spinal fluid picture It is particularly important to recognize the picture because approximately o per cent of the cases[6] of subacute bacterial

endocarditis have neurological symptoms or signs as their presenting complaint The cerebrospinal fluid findings are as follows, pleocytosis (100-1 000 cells per cu mm) chiefly polymorphonuclear cells occasionally a few or many red blood cells (50-1 000 per cu mm), increased protein content (50-125 mgm per cent), various abnormalities in the gold sol curve, normal sugar content and negative cultures

Poliomyelitis (acute anterior poliomyelitis) is associated with the following cerebrospinal fluid abnormalities, pleocytosis, which is higher in the pre-paralytic stage and falls rapidly after the onset of paralysis with an average count of about 160 white blood cells per cu mm at the time of onset of paralysis and about 35 white blood cells per cu mm two weeks later and a normal or slightly increased protein content at the time of onset of paralysis rising to an average of 150 mgm per cent three weeks later It should be noted that a marked albumino cytologic dissociation may be found in the fluids of patients with anterior poliomyelitis several weeks after the onset of the disease A high percentage of polymorphonuclear cells up to 50 per cent, is found early in the course of the disease and in patients with a high cell count About 20 per cent of patients show a mid-zone gold curve The sugar content is normal in this disease as in others caused by a filterible virus

With *herpes zoster* cerebrospinal fluid abnormalities are a mild pleocytosis (usually 5-50 white blood cells per cu mm, chiefly lymphocytes) and an increased protein content 50-100 mgm per cent in about half the patients The spinal fluid changes may precede the cutaneous eruption

Rabies is associated with the following cerebrospinal fluid abnormalities, pleocytosis (5-3 000 white blood cells per cu mm), normal or slightly increased protein content (30-90 mgm per cent) and an occasional mid-zone or first zone gold curve Encephalomyelitis following administration of anti rabitic vaccine is presumably the same etiologically as spontaneous or accidental rabies The spinal fluid findings associated with encephalomyelitis following anti-rabitic vaccine are essentially the same as those associated with rabies

Encephalitis lethargica (epidemic encephalitis, von Economo's encephalitis) is associated with the following cerebrospinal fluid findings, the pressure is normal there is a slight pleocytosis which disappears after the first few weeks and rarely exceeds 100 white blood cells per cu mm protein content is normal or slightly increased (rarely as high as 100 mgm per cent) sugar content is of course normal (the idea originally current that it was frequently increased is erroneous) chloride

content is normal and the colloidal gold test shows a mid zone curve in an occasional patient The diagnosis of epidemic encephalitis is rarely tenable at the present time

Eastern equine encephalomyelitis is a disease of horses but small epidemics of the disease have occurred in humans The cerebrospinal fluid abnormalities associated with the illness are a mild to marked pleocytosis (25 to 1 000 per cu mm) with a high percentage of polymorphonuclear leucocytes and a moderate increase in the protein content *Western equine encephalomyelitis* is characterized by the same cerebrospinal fluid abnormalities as is the Eastern type[7]

The *St Louis* and *Japanese B types of encephalitis* were characterized by cerebrospinal fluid abnormalities similar to those found in encephalitis lethargica[7,8]

Trypanosomiasis is associated with pleocytosis of varying degrees (from 5 2 000 white blood cells per cu mm mainly lymphocytes) an increase in protein content (rarely over 100 mgm per cent) and frequently the presence of organisms in the cerebrospinal fluid

Toxoplasmosis[9] is associated with a moderate to marked pleocytosis (50-1 000 white blood cells per cu mm chiefly lymphocytes although not always so) the presence of red blood cells occasionally in large number normal or moderately increased total protein and normal sugar and chloride content Organisms may be found in the fluid

Meningism

Meningism is defined clinically as the presence of signs and symptoms of meningeal irritation headache stiff neck and Kernig s sign at the onset of any acute febrile disease No case should be diagnosed meningism in which there is actual infection of the meninges themselves or any infection close to the meninges If these diagnostic criteria are followed such cases will exhibit a uniform cerebrospinal fluid syndrome of increase in pressure normal cell count normal sugar content and normal colloidal gold reaction and decreased protein and chloride content

Aseptic Meningeal Reaction

Aseptic meningeal reaction is a term often used to designate the inflammatory response in the leptomeninges which results from infec

tion of nearby adjacent structures such as the nervous parenchyma, the extradural or subdural spaces, the dural or nasal accessory sinuses the bones of the skull, etc Such an inflammatory response may produce any or all of the following cerebrospinal fluid abnormalities, increased pressure, pleocytosis ranging from 5 to 5 000 white blood cells per cu mm with a predominance of polymorphonuclear leucocytes and slight to moderate increase in protein content rarely above 100 mgm per cent The sugar content is normal, the fluid is sterile, and of course the Wassermann reaction is negative The gold sol curve will show various abnormalities in about 20 per cent of the patients This combination of abnormalities often is distinguishable from acute purulent meningitis only by the normal sugar content and absence of bacteria and from acute syphilitic meningitis by the negative Wassermann reaction

Bacterial infections of the parenchyma may give rise to rapidly spreading necrosis of cerebral tissue and death 'acute cerebral abscess' or 'cerebral gangrene' If the infection is localized and walled off true abscess formation results The cerebrospinal fluid abnormalities associated with *cerebral abscess* are essentially those characteristic of any "aseptic meningeal reaction" (compare epidural infections) Since an abscess and the edema surrounding it constitute a space-occupying lesion the pressure is likely to be particularly high If the abscess ruptures into a ventricle or into the subarachnoid space, the patient's condition changes dramatically for the worse and simultaneously the cerebrospinal fluid becomes grossly purulent and the sugar content rapidly falls to a low level

Spinal extradural abscess is a true neurological emergency, and its early diagnosis and prompt surgical treatment are as imperative as those of perforated peptic ulcer In performing lumbar puncture, when this diagnosis is suspected one should introduce the needle below the presumable level of the abscess In addition the stylet should be withdrawn repeatedly as the needle is advanced If pus appears the diagnosis is established the needle is withdrawn and the abscess is to be drained surgically If puncture is performed below the level of the abscess as intended the cerebrospinal fluid abnormalities are as follows partial or complete dynamic block in nearly every case pleocytosis in the majority of cases which may range from 5 - - 000 white blood cells per cu mm with predominance of polymorphonuclears high protein (almost always above 100 mgm per cent) and normal sugar Operation should be performed immediately after the diagnosis is established, as

every hour of delay increases the likelihood of permanent and irreparable damage to the spinal cord

Osteomyelitis of the skull secondary to fracture or sinus disease usually produces no change in the cerebrospinal fluid unless an extradural abscess is formed or a dural sinus infected The latter is quite common in patients with mastoiditis untreated or uncontrolled by sulfonamides or penicillin and is accompanied by changes in the cerebrospinal fluid already described under the terms sympathetic meningitis or aseptic meningeal reactions

Osteomyelitis of the spine whether tuberculous or pyogenic will not produce cerebrospinal fluid abnormalities until collapse of the vertebrae has caused enough deformity of the spinal canal to produce complete or partial block with signs of cord compression or unless an epidural abscess has formed The cerebrospinal fluid changes in the former are then indistinguishable from those due to spinal cord tumor dynamic block elevated protein slight to moderate pleocytosis and progressive xanthochromia and the diagnostic differentiation is on the basis of x ray changes etc The cerebrospinal fluid findings in the latter have been considered already

Thrombosis of a cerebral venous sinus lateral sinus thrombosis etc as a result of infection is accompanied by changes in the cerebrospinal fluid as described under the term aseptic meningeal reaction (see previous description)

Subdural empyema[10] usually is secondary to frontal sinus infection It produces in the cerebrospinal fluid the changes characteristic of the so called aseptic meningeal reaction normal or increased pressure (up to 350 mm) pleocytosis (15 800 white blood cells per cu mm with 5 per cent or more polymorphonuclears) moderate elevation of protein (up to 190 mgm per cent) and normal sugar[10] Treatment is adequate drainage of the infected subdural space plus indicated bacteriostatic therapy

Vascular Disease

Arterial occlusion due to either *thrombosis* or *aseptic embolus* are indistinguishable on the basis of cerebrospinal fluid findings These findings are as follows normal pressure in 80 per cent of the cases rarely increased over 50 mm uniformly clear color except for a very rare bloody fluid normal cell count in 90 per cent of the cases normal or slightly increased protein content normal sugar and chloride content

and occasionally an abnormality of the gold sol curve usually of the mid zone type.

Intracerebral hemorrhage produces the following cerebrospinal fluid abnormalities: pressure over 200 mm. of water in 60 per cent. of the cases and above 400 mm. in 20 per cent.; fluid bloody in about 70 per cent. of the cases and clear in about 30 per cent.; slight or moderate pleocytosis in 30 per cent. with clear fluid; normal or slightly increased protein content in the same 30 per cent.; normal sugar and chloride content in nearly every case and various abnormalities in the colloidal gold curve, usually due to the presence of blood serum in the fluid.

Subarachnoid hemorrhage is characterized by the presence of uniformly bloody spinal fluid with red blood cell count ranging up to 3.5 million per cu. mm., almost always under greatly increased pressure. The presence of blood in the cerebrospinal fluid does not indicate whether the bleeding is the result of rupture of an aneurysm in the subarachnoid space or is secondary to escape of blood into the subarachnoid space or ventricular system from an intracerebral hemorrhage or cerebral trauma.

Cerebral arteriosclerosis usually is not associated with cerebrospinal fluid abnormalities unless there is some complication such as cerebral thrombosis or hemorrhage, congestive heart failure or uremia. A slight pleocytosis (5-25 white blood cells per cu. mm.) is present in about 15 per cent. of the patients and a slight increase in the protein content (45-80 mgm. per cent.) in about the same proportion of patients. *If a patient has an initial pressure greater than 200 mm. of water* despite the fact that he is well relaxed and has a normal systemic venous pressure one should be extremely cautious about attributing his neurological signs or symptoms to cerebral arteriosclerosis.

Tumors of Central Nervous System

Brain tumor typically is associated with increased pressure and an increased protein content. About 30 per cent. of patients will show a normal pressure or a normal protein content or both, and a similar percentage will show a slight or moderate pleocytosis (5-100 white blood cells per cu. mm.). Very rarely a marked pleocytosis may be found, particularly if the tumor is close to one of the lateral ventricles or the third ventricle. Of all brain tumors acoustic neuromas are the most likely to show a high protein content (above 100 mgm. per cent. in 85 per

cent) It is not possible to differentiate between primary and secondary i e metastatic, brain tumor on the basis of the spinal fluid examination

Spinal cord tumors typically produce a partial or complete dynamic block below the level of the tumor In the absence of such a block diagnosis is rarely justifiable although such cases have been reported If the block is complete the fluid below it will be yellow in color and contain a large amount of protein If the block is partial the fluid will be clear and the protein content only moderately elevated It is not possible to differentiate on the basis of cerebrospinal fluid abnormalities between intradural, extradural and intramedullary spinal cord tumors

Trauma

Craniocerebral trauma may result in blood in the cerebrospinal fluid due to contusion or laceration of the brain or laceration of one or more meningeal vessels The pressure also may be elevated either because of cerebral edema or accumulation of blood

Extradural hematoma is associated with a high cerebrospinal fluid pressure If there has been coincident damage to the brain or lepto meninges the fluid is bloody if not it is clear and colorless Subdural hematoma is the most difficult complication of trauma to diagnose or exclude If the cerebrospinal fluid is examined within a week of the time of injury it will be found to be bloody and under an increased pressure unless the patient is dehydrated or has had several previous punctures Later the cerebrospinal fluid is xanthochromic and after several weeks it is clear and colorless At this stage the pressure may or may not be elevated but diagnosis is extremely difficult unless it is so If the fluid is clear the protein and cellular content will be normal Bloody or xanthochromic fluids may have an increased cell count and increased protein content as the result of the blood itself and the reaction of the meninges to the blood An increased cerebrospinal fluid pressure is in favor of the diagnosis of subdural hematoma in a patient with a clinical picture compatible with this diagnosis On the other hand the finding of a low or normal pressure does not exclude the diagnosis

Spinal fracture or dislocation may distort the spinal canal sufficiently to cause partial or complete dynamic block and an increased protein in the fluid below the level of the block In such cases prompt laminectomy must be seriously considered

Herniation of an intervertebral disc is associated with elevation of

cerebrospinal fluid protein in about 50 per cent of cases and rarely, with partial or complete dynamic block[11, 12] Protein values higher than 100 mgm per cent are against the diagnosis of ruptured disc

Diseases of Nervous System of Unknown Etiology

Multiple sclerosis is associated with the following cerebrospinal fluid abnormalities slight pleocytosis (5-50 white blood cells per cu mm) in 30 per cent of patients slight to moderate increase in protein content (rarely over 100 mgm per cent) in a similar percentage of patients and a first- or mid zone gold curve in about 50 per cent of patients An entirely normal spinal fluid is present in only about 30 per cent of patients with multiple sclerosis

Acute encephalomyelitis, neuromyelitis optica, etc, which in many patients probably represents an acute attack of multiple sclerosis, is associated with the following cerebrospinal fluid abnormalities mild or moderate pleocytosis (10 200 white blood cells per cu mm) slight to moderate increase in protein content in 60 per cent and a mid zone or first zone gold sol curve in a similar percentage

Schilder's disease produces cerebrospinal fluid abnormalities which are essentially the same as those described for multiple sclerosis *Syringomyelia* is associated with the following cerebrospinal fluid abnormalities slight to moderate increase in protein content (rarely above 100 mgm per cent) in 50 per cent of patients and slight pleocytosis (5-20 white blood cells per cu mm) in 15 per cent of patients Occasionally the syrinx becomes wide enough to produce a spinal block in which case the dynamic tests reveal the usual absence of response to jugular compression and the protein in the spinal fluid below the block is markedly increased Such cases can be differentiated from spinal cord tumor only by operation

Friedreich's ataxia usually produces no cerebrospinal fluid abnormalities Occasionally a slight lymphocytosis or increase in protein is found *Amyotrophic lateral sclerosis* and *progressive muscular atrophy* ordinarily produce no cerebrospinal fluid abnormality except that the protein content is increased in about one third of the patients (rarely above 75 mgm per cent) *Neuritic muscular atrophy, Charcot Marie-Tooth form of muscular atrophy*, usually produces no abnormality of the cerebrospinal fluid Occasionally there may be a slight increase in the protein content

Epilepsy, convulsive seizures cause unknown usually is associated with entirely normal cerebrospinal fluid Five to 10 per cent of the patients may show a slight increase in pressure (180 250 mm) an increased protein content (45 75 mgm) or slight pleocytosis The diagnosis of idiopathic epilepsy should be made with caution in any patient with an abnormality in the cerebrospinal fluid

Polyneuritis occasionally may follow a mild generalized infection and for that reason as well as because of the nature of its onset it is often called infectious polyneuritis although no etiological agent has ever been isolated Such patients often present a clinical picture somewhat different from other forms of polyneuritis in that the facial nerves are involved also facial diplegia These cases have been described under the term Guillain Barre syndrome The cerebrospinal fluid pressure usually is normal and the fluid cell free (occasionally 5-25 cells may be found), but the protein content usually is moderately or greatly increased (up to 750 mgm per cent) and there is a mid zone or occasionally an end zone gold sol curve Because of the high protein content the cerebrospinal fluid from these patients frequently is yellow in color Albumino cytological dissociation although usually present is not diagnostic since it may be present in anterior poliomyelitis during the convalescent stage as well as in other conditions

Intoxications of Central Nervous System

Lead poisoning may cause either polyneuritis or encephalopathy In patients with polyneuritis the cerebrospinal fluid usually is normal although a small percentage of patients show a slight increase in protein and occasionally an abnormal gold sol curve Patients usually infants with lead encephalopathy generally have marked abnormalities in the cerebrospinal fluid the pressure is elevated sometimes up to 1 000 mm of water the fluid occasionally is yellow the white blood cell count varies from normal to several thousand cells per cu mm although the pleocytosis usually is mild to moderate the protein content usually is increased often above 100 mgm per cent and the colloidal gold reaction may show any type of curve Chemical examination of the cerebrospinal fluid will show the presence of lead

Arsenic like lead may produce a polyneuritis but the organic arsenicals which are used routinely in the treatment of syphilis may produce also a hemorrhagic encephalitis Patients with arsenical neuritis

generally have a normal spinal fluid except for an increase in the protein content. Patients with hemorrhagic encephalitis generally have normal or moderately increased pressure (up to 250 mm.) and occasionally a slight pleocytosis or slight to moderate increase in protein content. Cerebrospinal fluid from such patients usually does not contain red blood cells.

Mercury may produce also a polyneuritis. The cerebrospinal fluid findings are essentially the same as those described in the cases due to lead or arsenic.

Carbon monoxide poisoning ordinarily produces no changes in the cerebrospinal fluid. Occasionally one finds a moderate increase in pressure and slight pleocytosis, or increased protein content also may be present.

Bromides and *other sedative drugs* usually produce no change in the cerebrospinal fluid except for the presence of the drug in the fluid, the detection of which requires a special test and ordinarily constitutes the evidence by which the diagnosis is established. Acute poisoning with bromides and other drugs such as morphine or barbiturates also is associated ordinarily with normal cerebrospinal fluid findings, although the pressure may be high if the respiratory rate is low and slight pleocytosis or increased protein content may occur.

Diseases not Primarily of Nervous System but in which the Nervous System may be Affected

Spirochetal jaundice (Weil's disease) produces the following abnormalities in the cerebrospinal fluid: a clear or yellow colored cerebrospinal fluid depending on the severity of the jaundice, pleocytosis of slight or moderate degree and a slight increase in protein content.

Undulant fever is associated with the following abnormalities in the cerebrospinal fluid: increased pressure, moderate degree of pleocytosis (25-400 white blood cells per cu. mm.) and moderate to marked increase in protein content. The organisms frequently can be cultured from the spinal fluid.

Tick borne relapsing fever (Treponema recurrentis) has been reported to produce signs of meningeal inflammation in about 25 per cent of cases[13]. In these cases the cerebrospinal fluid abnormalities were increased pressure and slight to marked pleocytosis (as high as 2,000 white blood cells per cu. mm.)

Post diphtheritic polyneuritis may be associated with a slight to moderate increase in protein content (up to 3 5 mgm per cent) and occasionally, a mid zone colloidal gold curve

Rickettsial infections in humans (European typhus, Mexican typhus Rocky Mountain spotted fever and tsutsugamushi fever) may be accompanied by a meningeal reaction with the following abnormalities in the cerebrospinal fluid slight to moderate pleocytosis (5 250 white blood cells per cu mm) slight to moderate increase in protein content (45 200 mgm per cent) and an increased pressure

Any of the *acute exanthemata* (variola varicella vaccinia rubeola rubella) may be followed rarely or occasionally by an encephalomyelitis In such cases the cerebrospinal fluid shows a normal or increased pressure slight to moderate pleocytosis (5 300 white blood cells per cu mm) a normal or increased protein content (up to 50 mgm per cent) a normal or mid zone gold sol curve and of course, normal sugar and chloride content

Virus pneumonia rarely may be complicated or followed by encephalomyelitis In one such case observed by the authors the pressure was normal on each of six lumbar punctures The cell count varied from 7 to 115 white blood cells per cu mm and the total protein varied from 66 to 330 mgm per cent These six punctures were all done in the first month of the disease Two and one half months after the onset the only abnormality in the cerebrospinal fluid was a total protein of 167 mgm per cent

Dengue fever often is associated with signs of meningeal irritation These signs and symptoms are said to be relieved by lumbar puncture and the cerebrospinal fluid findings reported in such cases are consistent with meningism[8]

Malaria may directly affect the central nervous system (cerebral malaria) Such cases usually are due to *P falciparum* (estivo autumnal malaria) In one report on 12 cases[14] the cerebrospinal fluid was regularly under increased pressure and pleocytosis was present in those cases manifesting marked meningeal symptoms In another report on 53 patients[15] the pressure was normal in the majority of patients and the cerebrospinal fluid was entirely normal except for one case with frankly bloody fluid attributed to a subarachnoid hemorrhage

The biologically false tests for syphilis which are found not infrequently in the serum of patients with malaria are not accompanied by a positive test in the cerebrospinal fluid[16]

Trichinosis usually produces no change in the cerebrospinal fluid

Occasionally there is a slight pleocytosis and increased protein content, and motile organisms may be found free in the cerebrospinal fluid

Cysticercus infection may produce the following cerebrospinal fluid abnormalities, the pressure usually is high, fluid occasionally is xanthochromic, there is moderate pleocytosis (up to 300 white blood cells per cu mm) protein content is moderately or markedly increased and an abnormal colloidal gold curve of any type may be present Fragments of the parasites or the cyst wall may be seen occasionally

Combined system disease generally is associated with pernicious anemia and usually produces no change in the cerebrospinal fluid An occasional slight pleocytosis (5-10 white blood cells per cu mm) is seen as well as an increase in protein content (45-95 mgm per cent) in about 20 per cent of patients

Polyneuritis in patients with *chronic alcoholism* is presumably due to deficiency in vitamin B complex and is supposed to be indistinguishable from the polyneuritis found in *beri-beri* In such cases the cerebrospinal fluid ordinarily is normal About 10 per cent of cases will show a slight pleocytosis (up to 25 white blood cells per cu mm) and about 15 per cent a slight or moderate increase in protein up to 100 mgm per cent

Pellagra may be associated with polyneuritis In such cases the cerebrospinal fluid syndrome is similar to that found in alcoholic or vitamin B deficiency neuritis

Diabetes mellitus will cause alterations in the cerebrospinal fluid sugar content proportionate to the blood sugar content If the latter is high the former will be so also If the latter is low (insulin shock), the former will be too When there is an accompanying polyneuritis the protein content may be elevated (50 to 200 mgm)

Hyperthyroidism produces no abnormality except a diminution of protein content in the cerebrospinal fluid

Myxedema produces the following abnormalities in the cerebrospinal fluid, a pressure of 200 mm or above is not uncommon a slight pleocytosis may be seen (up to 10 white blood cells per cu mm), the protein content is nearly always increased (up to 240 mgm per cent), and a mid-zone colloidal gold curve is found in about 25 per cent of cases

Acute nephritis may be associated with the following abnormalities in the cerebrospinal fluid the pressure may be as high as 500 600 mm particularly in the presence of edema the protein content is not abnormal but a first- or mid zone gold sol curve is found in 50 or 60 per cent of the patients

Nephrosis is associated with increased pressure slight pleocytosis (6 8 white blood cells per cu mm) and a mid zone colloidal gold curve in about 50 per cent of patients

Uremia is associated with the following cerebrospinal fluid abnormalities increased pressure in 80 per cent slight pleocytosis in 20 per cent a slight increase in protein content (45 150 mgm per cent) in 40 per cent increased chloride content (750 900 mgm per cent) in 50 per cent and mid zone colloidal gold curve in 10 per cent In addition there is an increase in the nonprotein nitrogen in the fluid

Jaundice of moderate or severe degree generally is associated with a yellow color in the cerebrospinal fluid The nature of the pigment responsible for this color is not known

Paget's disease is not associated with abnormalities in the cerebrospinal fluid unless there are signs of involvement of the cortex cranial nerves or spinal cord In such cases there may be increase in the protein content of the cerebrospinal fluid and rarely an increase in the pressure If the vertebral involvement is sufficiently severe to cause spinal subarachnoid block the usual changes in the fluid below the level of the block will be present

Any *condition, which causes a rise in systemic venous pressure,* will produce a corresponding rise in cerebrospinal fluid pressure Such conditions include right sided heart failure pericarditis with effusion constrictive pericarditis and occlusion of either the superior or inferior vena cava No other abnormalities are present in the cerebrospinal fluid in any of these conditions

Leukemia occasionally may involve the central nervous system In the patient in whom there are signs of central nervous system involvement cerebrospinal fluid abnormalities include increased protein (up to 400 mgm per cent) and pleocytosis (up to 8 000 white blood cells per cu mm the cells being leukemic cells) in 41 per cent Cases have been reported of spinal subarachnoid block associated with leukemia

Infectious mononucleosis occasionally shows signs and symptoms of involvement of the central nervous system In such cases the cerebrospinal fluid shows mild pleocytosis and a slight increase in the protein content

Diseases of Nervous System with Normal Cerebrospinal Fluid

The following diseases of the central nervous system are unassociated with any abnormality in the cerebrospinal fluid amyotonia congenita

Bell's palsy, botulism, cerebral diplegia, dystonia musculorum deformans Huntington's chorea Leber's disease (familial optic neuritis) mental deficiency migraine myasthenia gravis, myotonia dystrophica, narcolepsy, otitic vertigo (Ménière's disease), periodic familial paralysis progressive muscular dystrophy, retinitis pigmentosa, tetanus and trigeminal neuralgia

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